The Role of Psychosocial Factors in The Progression and Recurrence of Illness: A Study Of Herpes Virus Infectious Illness And Chronic Fatigue Syndrome

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ABSTRACT

There is now a body of research that has investigated associations between psychosocial factors and viral illnesses. This research has examined both effects of viral illnesses on psychological distress and also psychosocial pre-cursors to infection. The studies reported in this thesis investigated whether the reactivation of herpes viruses was associated with psychological distress and with the occurrence of upper respiratory tract infections. The aims were to determine whether reactivated herpes virus infections induced psychopathology and whether specific psychological states, such as increased stress, preceded the viral illness. By measuring the occurrence of upper respiratory virus infections (URTIs) it was possible to examine whether herpes infection and conditions that have been associated with it (e.g. chronic fatigue syndrome [CFS]) have an immunological cost that leads to a greater risk of infection with other viruses.

The first study investigated psychosocial factors and Infectious Mononucleosis. A cross sectional analysis found significant differences between both the acute and chronic glandular fever sufferers and controls on a range of measures of psychological distress. In addition, IM sufferers reported significantly more frequent URTIs than controls which could be an indication that immunosuppression is a factor in this illness. A longitudinal study of the viral illness proved to be difficult but this approach was adopted in a study of cold sore sufferers.

The cross sectional analysis showed significant differences in psychosocial factors between the cold sore sufferers who experienced regular recurrences of cold sores compared with those who experienced few recurrences. These differences were maintained when both negative affect and previous illness was co-varied. Those suffering *frequent* recurrences experienced greater distress than those only suffering an occasional recurrence. The longitudinal analysis investigated the causal relationship between psychological variables and the cold sores recurrence. There were significantly higher stress scores in the weeks prior to an outbreak compared to weeks when there was no subsequent outbreak.

The final study confirmed significant differences between CFS patients and controls on a range of psychological measures of stress and depression. The longitudinal analysis showed that psychological stress and negative mood were significantly associated with the subsequent recurrence of both symptoms of fatigue and URTIs.

The longitudinal studies in this thesis found evidence for a causal relationship between psychological stress/negative mood and the subsequent recurrence of latent herpes virus and URTIs in chronically ill participants. These effects were much clearer than associations between stress and infection in volunteers with no chronic illness and it is possible that the latent infection leads to an immunological cost which in turn means a greater risk of URTIs.

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CHAPTER 1

1.1 Introduction to the Thesis

1.2 Background and Rationale

The aim of this thesis was to further develop an understanding of the relationship between psychosocial factors, in particular psychological stress, and infectious illness. In order to do this, specific infectious illnesses were selected for investigation and the reason for this selection is outlined below. The framework for the methodology used in these investigations is based upon the model of stress developed by Lazarus (1966). This model provides the rationale for the inclusion of specific variables, and the methodology used in these studies, and is described more fully below.

The aims of this introductory chapter are:

1. To introduce some of the issues and difficulties associated with the conceptualization of stress and provide a rationale for the model of stress adopted and the related methodology used in these studies
2. To summarize the literature regarding stress and infectious illness and to provide a rationale for further investigations in this area and for the choice of illnesses selected
3. To summarise the main aims and methods used in this thesis

1.3 Models of Health and Illness

Despite considerable evidence that psychological state plays a significant role in the etiology and progression of certain somatic complaints, either directly through stress induced physiological changes or indirectly through behavioral changes that affect health (see Jemmott & Locke 1984), there has been a reluctance to abandon the medical model of health and illness. Western medicine, with its

roots in Cartesian mind/body dualism, fundamentally subscribes to the view that medicine should be concerned with the physical mechanics of the body with issues of the 'non tangible' mind left to the realms of philosophy. The changing pattern of illness, however, has proved problematic for the medical model due to its inability to fully explain how and why people develop the sort of chronic illnesses which are common in the early 21st Century.

Morbidity and mortality are now largely caused by non contagious diseases linked to behaviour or lifestyle. Rather than there being a single, easily identifiable 'cause' for these diseases, they are characterized by a multiple risk factor etiology. The risk factors are not only physical but include psychological and social factors as well. For example the main cause of death in western society is Coronary Heart Disease (CHD). There is no single cause of CHD but the risk of developing this disease increases as a consequence of a number of different risk factors which includes behavioral risk factors such as smoking and diet, genetic and physiological risk factors such as inherited vulnerability as well as psychological and social risk factors such as type A behavior and stressful life events.

The medical model also faces difficulties in explaining the way we understand the nature of illness. Challenges to the medical model, in part due to this difficulty in explaining the development and treatment of illness, has led to the development of a biopsychosocial model. Engels (1977) was one of the first to provide an extensive review of these challenges to the medical model, and also a clear rationale for adopting a biopsychosocial model of health and illness.

The biopsychosocial model is a more complex, holistic model of health and illness which considers interactions between psychological, biological and social factors in the onset and course of illness as well as in the conceptualization of health (Engel 1977). It provides a more comprehensive model for understanding the interaction of multiple risk factors in the development and progression of

illness and is more applicable to the understanding of health and illness than the medical model.

Whilst this model, initially, was applied to the understanding of major chronic diseases, particularly those associated with the central nervous system such as coronary heart disease, stomach ulcers, etc. it has now been expanded to embrace a broad range of illnesses, including infectious diseases. Explanations of the physiological mechanisms via which stress influences the body have developed over the past 40 years and stress research has increased our understanding of how psychological factors may be mediated via the central nervous system by, for example, increasing heart rate and triggering the 'flight or fight' response. Associations with particular diseases also were apparent. (e.g. Selye's General Adaptation Syndrome, 1985). Diseases associated with viral infections, perhaps because they were more easily explained using the medical model of illness, were not immediately conceptualized using the biopsychosocial paradigm. Infectious illnesses (where a specific identifiable pathogen invades the body causing a series of somatic symptoms which can normally be identified as a particular illness) fits very neatly into the Germ Theory of Illness (cited in Stone 1979) and questions regarding the role of psychological or social factors were not raised until recently when it became apparent that not everyone exposed to these pathogens actually developed the illness. Recent developments using the theoretical framework of psychoneuroimmunology (PNI) has increased our understanding of the relationship between stress and infectious disease and has provided evidence for an association between psychological factors and infectious illness, as well as a greater understanding of the physiological pathways which mediate this relationship. Many of the methodological difficulties associated with research using a PNI framework are related not only to the measurement of immune status but also to the conceptualization and measurement of stress.

1.4 Why study stress and infectious illness?

Perhaps one of the first important milestones in establishing the relationship between psychological factors and immune function was the now classic study by Ader and Cohen (1991) which demonstrated that immunosuppression could be classically conditioned in animals (see review in Ader 2001). Since then there have been numerous studies investigating:

1. The relationship between psychosocial factors and immune function
2. The relationship between psychosocial factors and immune related disease

There are now a number of reviews of the literature on the influence of psychological factors on immune function and the development and progression of specific viral illnesses (e.g. Jemmott & Locke, 1984; Cohen & Williamson, 1991; Cohen & Herbert, 1996; Segerstrom, S. & Miller, G.E. 2004). A selection of these studies is outlined below giving some indication of the current findings in the research into psychological factors and immune function.

1.5 Stress and Immunity

One way of examining any relationship between stress and immunity has been to study the immunomodulating effects of stress and there is now a growing body of evidence for the existence of this relationship. A number of studies have investigated a range of parameters of immune function.

Taking one example, Kiecolt Glaser and colleagues (1984) investigated the effects of a naturally occurring stressor on the immune response of a healthy population of medical students. Blood samples were taken one month before final examinations and again at the beginning of their examination period. The researchers found that natural killer cell (NK) activity declined significantly from the baseline measure to the stress measure. NK activity is an indicator of the cellular immune response, these cells are associated with anti-tumor and anti-viral

activity. They also considered the humeral immune response and took measures of immunoglobulin, including total plasma IgG, IgA, IgM and c reactive protein as well as salivary IgA. They found that plasma IgA increased significantly from time one to time two whereas plasma IgG and IgM, salivary IgA and crp did not. A broad range of other stressors have also been considered and a review of these studies may be found in Segerstrom (2004).

From these studies it may be concluded that the immune system is sensitive to even relatively mild stressors and a range of both naturally occurring stressors as well as laboratory stressors have been associated with a wide range of changes in immune function. However, there are a number of problems with this research and these are summarized below.

1. It is highly intrusive; a range of measures of immune functioning are required and this necessitates repeated sampling of blood and other body fluids which in itself may be very stressful.
2. A range of immune measures need to be sampled because, as indicated above, changes may occur in one aspect of immune function but not in another and furthermore increased activity in one area may be associated with decreased activity in another.
3. The relationship between immune suppression and illness is not fully understood and so the implications of stressor induced immune changes for disease susceptibility are not clear.

What is also required then is a consideration of the role of psychosocial factors in diseases in which abnormalities in immunologic state are thought to be important, infectious diseases clearly fall into this category.

1.6 Stress and Infectious Illness

The occurrence of specific infectious diseases as a function of a variety of psychosocial factors has received some attention. There are three aspects of the disease process that have been investigated:

1. Primary infection with the pathogen (i.e. are those who are suffering higher levels of psychological stress or who experience greater negative life events more likely to develop an infectious illness than those who are less stressed?)
2. Duration and severity of the illness (i.e. do those higher in psychological stress suffer more severe symptoms of illness, and suffer for a longer period, than those who are less stressed?)
3. Recurrence of the illness in latently infected hosts (whereby psychosocial factors may be involved in the reactivation of latent viruses via suppression of the immune defense mechanisms)

When exposed to an infectious agent, only a proportion of people develop clinical disease and there appears to be wide variation in the severity and symptomatology among those who do become ill. Clearly, the primary infection with a pathogen is dependent upon being exposed to the infectious agent. In studies of primary infection, controlling for exposure to the virus can be problematic. In naturalistic studies it is not possible to know exactly who has been exposed and who has not. Some of the few investigations controlling for exposure were conducted by Cohen, Tyrell and Smith (1991; 1993). In these viral challenge studies, participants were quarantined and either given a nasal drop containing a specific virus (one of five different respiratory viruses) or placebo. Researchers found that increased reported levels of psychological stress was associated with an increased risk of acute infectious respiratory illness in a dose response manner. They were able to establish that the relation between stress and

colds was associated with host resistance and not with differential exposure to the virus.

The association between stress and infection held up for all the viruses tested including rhinovirus, coronavirus and respiratory syncytial virus. This suggestsed that stress was associated with the suppression of a general resistance process in the host, leaving persons susceptible to multiple infectious agents. This study also controlled for the potential effect of health risk behaviours including smoking, alcohol consumption, exercise, sleep and diet. The association between stress and illness was found to be independent of these health behaviours. The results showed that high levels of reported psychological stress was associated with an increased risk of developing the illness in a 'dose response manner' (i.e. as stress increased so did the likelihood of developing the disease).

1.7 Limitations of the Research

There are a number of reviews of studies investigating naturalistic stressors as well as laboratory stressors and their relationship to infectious illness; however, despite evidence demonstrating a relationship between a range of stressors and a range of infectious illnesses there continues to be a number of problematic methodological issues that needs to be addressed in this area. Cohen and Williamson concluded that "Further pursuit of this question is justified – especially work using designs that allow us to address numerous remaining ambiguities and unanswered questions" (Cohen & Williamson 1991; Page 20) Cohen and Herbert (1996), in reviewing studies of the relationship between depression and immune related disease, argued that although this area has received considerable attention, there is much variability in the findings which is largely due to methodological differences. They argue that few studies use control groups matched for age and gender. In relation to studies specifically of stress and infectious disease they conclude that whilst there is general support for the relationship, "the evidence is not entirely consistent and methodological

limitations warrant cautious interpretation of these results. Moreover, most existing work does not establish the extent to which such effects are mediated through immune or behavioural pathways" (p. 113). Segerstrom (2004) in a meta-analytic study of 300 articles on psychological stress and immunity argues that what should be considered in future research in this area are individual differences in vulnerability to stressors. She suggests that disease status is one factor which may increase immune related vulnerability to stress and suggests that this is something that should be considered in future research. She also points out that individual differences in the subjective experience of stress is an important factor and she states that few of the studies reviewed included measures of subjective experience of stress. Future research she suggests needs to consider cognitive appraisal of stressors in its design.

1.8 Stress and Recurrence of Latent (Herpes) Virus

In the investigations reported in this thesis I have chosen to adopt the third approach to investigating stress and infectious illness. This approach focuses on the relationship between psychosocial factors and the reactivation of latent viruses. The infectious illnesses selected are part of the family of herpes viruses in which the infected individual remains latently infected for life after the primary infection. (Glaser and Gotlieb-Stematsky, 1982). Unlike other common viruses, those infected with herpes virus remain latently infected and when immunity is compromised in some way reactivation of the latent virus can occur, resulting in disease. Both cellular and humeral immunity is believed to be important in the control of herpes virus infections although cellular immunity appears to be more important (Kiecolt Glaser, cited in Kurstak et al., 1987).

Studying latent viruses such as this enables the researcher to overcome the problem of controlling for exposure to virus as well as problems associated with the measurement of immune function. The assumption is that psychosocial factors are involved in the reactivation of the latent virus through suppression of

the immune defense system. The aim in the studies reported in this thesis was to investigate whether those higher in psychological stress suffered more recurrences and whether reactivation of the virus was associated with higher levels of psychosocial factors and/or psychological stress. There appear to be substantial unexplained differences between people in the course of reactivation of latent viral infections. Reasons for this variability in response are not well understood and the possibility that psychological factors play a role is worthy of further investigation.

There are Five human herpes viruses which are listed and described in Table 1 below:

Table 1: Description of the five Human Herpes Virus

Type	Clinical Manifestations	Site of Latent Infection
Herpes Simplex type 1 (HSV-1)	Cold sores, neonatal herpes	Trigeminal nerve
Herpes Simples type 2 (HSV-2)	Genital infections, neonatal herpes	Sacral nerve
Cytomegalovirus (CMV)	Mononucleosis Syndrome, mental retardation and deafness in neonates	Not established, possibly lymphocytes
Varicella Zoster (VZV)	Chicken Pox (Primary Infection) Shingles (recurrence)	Neurons, multiple tissues
Epstein Barr Virus (EBV)	Infectious mononucleosis, B-cell lymphoma, Burkitt's lymphoma, nasopharyngeal carcinoma.	B Lymphocytes, epithelial cells.

NB: adapted from Kiecolt Glaser (1987)

This research in this thesis is concerned with Epstein Barr Virus and Herpes Simplex Type 1. In addition, the research examined upper respiratory tract infections in patients with Chronic Fatigue Syndrome (CFS), a condition that may develop following EBV infection.

1.8.1 Epstein Barr Virus (EBV)

The first illness investigated in this thesis was infectious mononucleosis, caused by the Epstein Barr Virus. Infectious Mononucleosis (IM), or glandular fever as it is more commonly known, can be a severely debilitating disease which usually affects young adults. What is particularly interesting about IM is the fact that whilst most people recover from the initial illness after about six to eight weeks, there is a great deal of variability in the severity and the pathogenesis of this illness. A number of people become severely incapacitated, and some people fail to recover for many years following the initial infection. As discussed earlier, an interesting aspect of latent viruses such as this is that they can recur as a result of anything that compromises immunity because a feature of this family of viruses is that they are never completely eradicated but lie dormant in the body after initial infection. Whilst it is clear that reactivation of these viruses occurs during serious immunocompromising conditions, such as AIDS, it is less clear whether those who fail to recover from the initial infection are suffering reactivation of the initial virus, susceptibility to other viruses or a continuous immunosuppression resulting in continued high levels of the main symptoms. It is also a possibility that psychological stress and/or high levels of anxiety could influence both the perception of symptoms and the reporting of illness and failure to recover may be a purely psychological phenonomenon.

There have been a number of studies which have considered the role of psychosocial factors in the development of this disorder, and these are reviewed in the next chapter.

Studies of the role of psychosocial factors in either the onset or recurrence of this disease have provided contrasting results. In some, psychological stress appears to be associated with initial infection and reactivation but in others the findings are more ambiguous. More recent research, such as White (1995), has provided

clear evidence of a fatigue syndrome following glandular fever, an issue which will be returned to later in the thesis.

There is a need to further investigate the role of psychosocial factors in the pathogenesis of glandular fever in order to more fully understand both the psychological consequences or after effects of this disorder as well as to consider differences between those in the acute stage of the illness compared with those with the more chronic condition (i.e. those who have failed to recover or who are suffering a recurrence of the main symptoms of this illness). This study controlled for negative affectivity, a major bias in reporting subjective characteristics and health status as a consequence of psychological stress and anxiety. In addition, the incidence of upper respiratory tract infections was recorded as this may be an indicator of immune system status.

The main aims of the glandular fever study were:-

1. To investigate the psychological and physical effects of this illness in both the acute and chronic stages. This cross-sectional investigation aimed to compare glandular fever sufferers with a healthy control group on a range of standard psychosocial measures of objective and subjective stress, mood, depression, self esteem, coping strategies and social support as well as on physical well being including current symptoms, recurrence of other illness, cognitive difficulties and fatigue related symptoms. As well as investigating differences between the control group and the glandular fever groups (acute and chronic), the aim was also to make comparisons between those in the acute and chronic stages of the illness. This study ensured that the role of negative affect was controlled and that the groups were matched on relevant health risk behaviors, known to confound this type of analysis.

2. To more fully understand the subjective experience of those suffering from this illness and their perspectives regarding the progression of this illness over time including the recurrence of symptoms of glandular fever and the recurrence of other infectious illness.

3. One of the initial aims of this thesis, to investigate the relationship between psychosocial factors and the progression of this illness longitudinally. The aim was to investigate the role of psychological factors in the progression and recurrence of symptoms of illness. This aim, however, was marred by some practical difficulties, explained more fully later in the thesis, and therefore the decision to study a more frequently recurring herpes virus (Herpes Simplex I) was considered.

1.8.2 Herpes Simplex Type 1

The study of Herpes Simplex overcame some of the problems experienced with the first investigation. Firstly, the reactivation of the virus could be clearly and easily verified because its appearance is usually obvious. Secondly, there is a large variation in the frequency of recurrence with some people suffering frequent recurrences over a relatively short period of time. The methodology from the glandular fever study was adopted and applied to the study of herpes simplex. For the longitudinal part of this investigation, more frequent (i.e. weekly) measurements of the relevant variables were required and a diary methodology was developed and used.

A number of retrospective and prospective studies have investigated the role of mood, psychological stress and social support in the recurrence of this virus. As in studies of IM the results are discordant, in particular the role of psychological stress is ambiguous.

Furthermore, many of the studies do not control for the possible confounding effect of health risk behaviors, negative affect, previous and current illness. A review of this research is provided in chapter 2. For the longitudinal section of this study, a diary methodology was used to collect information weekly over a 16 week period.

The aims of the herpes simplex studies were:-

1. To compare those suffering from oral/facial herpes virus (i.e. the cold sore group) with a healthy control group on measures of objective and subjective stress as well as other psychosocial variables including depression, mood, self esteem, coping strategies and social support, controlling for the confounding effect of negative affect, health risk behaviors, current and previous illness.
2. The study also aimed to compare the groups on physical well being, current symptoms, cognitive difficulty and recurrence of other infectious illness.
3. The longitudinal study aimed to investigate the recurrence of both cold sores and other infectious illness over time; more specifically, to investigate the role of negative mood and psychological stress in the recurrence of herpes simplex, i.e. are outbreaks of cold sores preceded by negative mood and/or psychological stress?
4. This methodology proved to be effective in the measurement of changes in stress, mood, symptoms and recurrence of infectious illness over time and it was decided to adopt this methodology in the next study.

1.8.3 Chronic Fatigue Syndrome

In the final study, the role of psychosocial factors in chronic post viral illness was considered in relation to Chronic Fatigue Syndrome (CFS). Following from the earlier study of Infectious Mononucleosis, it was decided to investigate the role of psychosocial factors and the recurrence of other infectious illnesses in CFS patients and to do so using a diary methodology similar to that used in the study of Herpes Simplex. Many of those suffering from CFS report that the illness was precipitated by the Epstein Barr Virus and there has been much debate in the literature regarding the precise role of Infectious Mononucleosis in the development of CFS and this debate is summarized in Chapter 7. The third and final study in this thesis investigated the role of psychosocial factors in the progression of CFS.

At the start of this study, Epstein Barr onset chronic fatigue sufferers were compared with chronic fatigue sufferers whose illness was not precipitated by Epstein Barr virus to determine whether there were differences that reflect the etiology of the disease. A cross sectional analysis examined whether there were psychosocial differences between chronic fatigue patients and healthy controls and compared the incidence of infectious illnesses in the two groups. It also examined similarities in the psychosocial status of chronic glandular fever sufferers and those diagnosed with chronic fatigue syndrome.

The longitudinal analysis considered the temporal relationship between weekly stress and negative mood and both the recurrence of the main symptoms of chronic fatigue as well as the recurrence of other infectious illness.

1.9 Methodological Issues

The present studies took into consideration a number of the problematic methodological issues which could account for previous inconsistent findings:-

1. The issue of negative affect influencing responses to questions regarding health and psychological well being were controlled in the studies in this thesis
2. The possible confounding effects of current and previous illness were, where possible, taken into consideration in the studies in this thesis
3. The role of behavioural responses to stress were considered (i.e. psychosocial factors may play a role in the progression of disease because the behavioural response influences immunity). People high in stress may smoke more, drink more alcohol, sleep less or have a poorer diet. The studies in this thesis consider these behavioural factors when investigating the link between stress and illness
4. Research in this area is dominated by studies using retrospective reports of stress and illness. Current illness is known to influence recall of stress and illness and over reliance on retrospective reports of illness, particularly in those who are currently ill, can produce biased results. The studies in this thesis did not rely wholly on retrospective reports of stress and illness but often used a prospective design.
5. The area is also dominated by correlational research and whilst some of the correlational research has been replicated in these studies (to confirm previous research findings were appropriate) longitudinal studies were used in order to develop our understanding of the cause and effect relationships between stress and illness

1.10 Conceptual and Methodological Issues in the Measurement of Stress

What do we mean by stress?

The term stress is widely used by both psychologists and lay people, although any attempt to arrive at a consensus as to its true definition continues to be elusive. An interesting anecdotal reference to its' definition was that stress 'in addition to being itself, and the result of itself, is also the cause of itself.' The stress literature in psychology refers to three main categories of stress:-

1. Stress as a stimulus, referring to the conditions that are likely to stimulate an emotional reaction.
2. Stress as a response referring to reactions to such situations which may be psychological or physiological.
3. Stress as a process in which a range of different components should be considered.

The evolution of the concept of stress has been very well documented by many researchers such as Lazarus, (1984) and Bartlett, (1998). Most stress researchers would now agree that an approach based purely on exposure to a stressor is insufficient to predict disease outcome. Individual differences in the way people respond to a particular stressor needs to be considered. The appraisal process (i.e. how the stressor is perceived and thought about) is a key issue; for example is the stimulus perceived as predictable, controllable and/or overloading? These questions comprise what Lazarus terms the primary appraisal process. The stress process (i.e. how the response to a stressor is perpetuated and maintained) is a constructive, ongoing activity. Primary appraisal is followed by the secondary appraisal process, whereby responses made to cope with or adapt to the stressor are instigated (i.e. attempts to change the situation, or to deny or ignore it) and the appraisal of outcomes (i.e. successful or unsuccessful) are made. These aspects of the stress process reflect the resources that individuals bring to the stress appraisal process that may be personal (i.e.involving characteristics of the

individual such as attitudes and beliefs, mood, self esteem or optimism) and/or environmental (e.g. perceived availability of support systems) as well as clutural . People appraise potentially threatening or challenging events in the light of, for example, past experience, social support or, coping resources. This perspective suggests that stressor effects occur only when both the situation is appraised as threatening and the individual believes that they have insufficient resources available to cope with the situation. This thesis adopts the psychological process model, as far as was practically possible, as the basis for understanding the relationship between stress and illness. On the basis of this model a number of different variables were taken into consideration in the measurement of stress, however most of the analyses simply considered a straightforward relationship between the variables (whilst co-varying potential confounding variables) rather than more complex interactions.

1.11 The Stress/Illness Relationship and the Measurement of Stress

The relationship between stress and illness continues to be a controversial and complex area of research and numerous debates revolve around the precise nature of the relationship between the variables. The relatively simple causal chain between stress and illness considers that those higher in stress will develop more illness than those lower in stress. The need to measure individual differences in the perception of stress has been discussed in relation to Lazarus's theory of cognitive appraisal, however, another conceptual problem in the stress literature is the issue of precisely which variables need to be measured in the stress/illness relationship and how they exert their influence. Considerable difficulties exist regarding the conceptualization of moderating or mediating variables in this relationship. Folkman and Lazarus (1988) describe moderator variables as antecedent conditions such as personality or socio-economic status that interact with stress to affect the outcome. These are stable variables which moderate the impact of stress upon health e.g. those higher in self esteem may be less vulnerable to the negative health consequences of stress than those low in self

esteem. Mediator variables, on the other hand, intervene in the stress health outcome chain. They are not separate antecedent entities but come into being as a consequence of exposure to stress, for example stress and illness may be mediated by health behaviours or coping strategies so that when someone is experiencing high stress they may, for example, seek social support to help them cope with the stressor. So the causal chain would be that stress influences health behavior or coping strategy which then renders the individual more (or less) vulnerable to illness. It may be argued that statistical techniques involving multiple regression modeling may be the optimum method of evaluating the mediating or moderating status of a number of relevant variables. In practice, this can be difficult due to the potentially large number of variables that would need to be entered into the model and, as a consequence, the large number of participants required in order to attempt this type of analysis. When focusing on groups of individuals suffering from specific illnesses (and thereby countering some of the methodological difficulties associated with outcome measures discussed later) it may be difficult, in practice, to recruit sufficiently large numbers of participants. This is particularly the case when using a 'community sample' (i.e. those not attending a clinic for treatment).

1.12 Analysis

The studies in this thesis relied largely on analysis of variance to demonstrate a range of individual differences between particular categories of participants. Analysis of co-variance was used where it was necessary to control for the potential confounding influence of relevant mediating or moderating variables. Furthermore, the groups in this thesis were shown not to differ in potentially confounding variables such as health behaviors and demographics. Finally, it should be noted that in trying to account for all the possible interactions between a large number of variables, the process of partialling out too many things at once could result in the removal of enough of the shared variance or degrees of freedom to eliminate the effect of that variable completely. In other words, it is

possible to eradicate the effect of any variable, even if there is a large effect, if enough alternative variables are put into the regression. Although the obvious confounding variables were controlled in these studies, an attempt to co-vary too many other variables has been avoided.

Problems regarding the measurement of stress can be applied to the measurement of health status. Traditionally in the literature, scores on stress scales are correlated with a number of outcome measures aimed at assessing health. Outcome measures used in this thesis include fairly detailed assessment of the nature and severity illness and/or of symptoms. One criticism leveled at this type of analysis is that highly stressed respondents will be more likely to indicate that they are suffering from a range of symptoms than a non stressed group. This has been overcome in this thesis by providing the participants with a wide range of potential symptoms to choose from. If their response to a symptom checklist was high simply as a consequence of stress one would expect the profile of symptoms to be higher across a range of symptoms rather than focused on specific symptoms indicative of a particular illness i.e. a specific, coherent cluster of symptoms. Secondly, differences in responses may constitute what is known as the 'neuroticism effect' (i.e. those high in neuroticism will score highly both on subjective measures of stress and subjective measures of health status). Furthermore, research in this thesis focuses on particular illnesses which makes the outcome measures more precise in that what is being considered is the recurrence of specific symptoms of the illness (in the case of cold sores specific and verifiable manifestations of the illness).

In this way some of the more common methodological difficulties associated with research into stress and illness have been addressed.

1.13 Selection of measures used

The model of stress adopted has implications for the measures selected for use in this thesis. This model of stress then requires a multivariate approach to the measurement of stress. Reliable measures of both the stimulus (i.e. stressors or antecedents) and the response pattern (i.e. illness progression, symptoms and psychological well being) were required, as well as of the perception of stress (how predictable, controllable and overloading is it) together with other variables which are relevant to the stress illness relationship including coping strategies, social support, personality characteristics and mood states.

An important issue associated with the measurement of stress is the distinction between reports of exposure to potentially stressful events and subjective reports of perceived stress. Reporting of stressful events has the advantage of being more reliable and less subject to confounding factors such as neuroticism, however, the earlier debate highlights the view that a stressor is only stressful if it is viewed as such More recently it has been argued that minor forms of stress, referred to as daily hassles, can have an equally negative effect on health, in particular when they are cumulative.(De Longis et al,.1982) All three aspects are measured in this thesis – life events with the additional requirement that participants indicate whether the life event was perceived as 'good' or 'bad'; the frequency and severity of daily hassles; and the perception of stress in terms of its controllability, predictability and overload.

The measures associated with the secondary appraisal process involves the measurement of coping and social support and the dispositional characteristics which are relevant to the stress process which were also measured in this thesis included negative affect, self esteem and locus of control. As well as a range of measures of illness, further outcome measures included depression cognitive difficulties, emotional difficulties fatigue and other symptoms

1.14 Cross Sectional versus Longitudinal Analysis

Although most researchers recognize the superiority of longitudinal designs, much information can also be obtained from cross sectional designs with measures taken at one point in time. The cross sectional analysis in this thesis compared sufferers of a particular illness with a control group who were matched on moderator variables but who were not suffering from the illness being investigated. It also considered differences between those suffering from an illness at different stages of that illness.

In the study of glandular fever, for example, participants in the acute and chronic stages were compared, as were those with the acute symptoms and those without the acute symptoms. This type of analysis may not allow any inference of causality however it can provide rich information regarding the relationship amongst the variables at different critical stages of the illness and interesting comparisons can be made. Other analyses in this thesis were longitudinal and specifically addressed the temporal relationships between the variables. One criticism of many longitudinal designs is that they only incorporate two measurement occasions and such limited observation periods make it difficult to gain any depth of insight into the nature of the stress process. In this thesis the longitudinal analyses incorporated weekly measurements of critical variables over a 4 month time period.

1.14.1 Model of Stress and Psychosocial Variables Measured

The main measures collected in the studies described here are shown below.

STRESSORS:	Major Life Events Minor Daily Hassles
STRESS APPRAISAL:	Perceived Stress
VARIABLES INFLUENCING: SECONDARY APPRAISAL:	Coping Strategies Social Support
DISPOSITIONAL: CHARACTERISTICS:	Mood Self Esteem Dispositional Optimism
CONFOUNDING VARIABLES:	Trait Anxiety Demographics Health Behaviors
OUTCOMES:	Depression Illness Measures Profile of Fatigue Related Symptoms (cognitive difficulty, emotional difficulty, fatigue and somatic symptoms)

The actual measures and scales used are fully described in the methodology section of the first study.

1.15 Self Report Questionnaires

The main mode of data collection was the use of questionnaires which were completed by the participants. Self report is the primary tool used by researchers for the measurement of stress and despite a desire for more 'objective' measures of stress (e.g. objective life event scales, biological markers, clinical ratings, and

independent observations of behaviours) all measures have their inherent problems and weaknesses. Despite criticisms of subjectivity of self report measures, they continue to be the most useful method of assessment in this area of research. Alternative validation of reports and objective measures were sought wherever possible. 'Objective' life events scales were used as well as more subjective perceptions of stress. Illness was verified either by writing to General Practitioners for confirmation of tests or, as in the case of cold sores, by observation of the reactivation of the virus. Validated measurement scales were used to measure the selected variables wherever possible; these scales were carefully selected to ensure reliability in measuring the variables of interest and with a view to the type of statistical analysis required. The reliability and validity of these scales is reported where appropriate.

1.16 Summary

The aim of this thesis was to consider the role of psychosocial factors in the progression and recurrence of latent viral infections as well as the recurrence of viral infections in people suffering from infectious mononucleosis, herpes simplex and chronic fatigue syndrome. Careful consideration has been given to previous methodological difficulties within this research paradigm; to the conceptualization and measurement of stress and to the selection and measurement of infectious illnesses to be studied and the best way of doing so. The studies in this thesis consider two herpes viruses that are characterized by their ability to subsequently recur following the primary infection. In addition, the incidence and severity of upper respiratory tract illnesses in the different groups of participants were examined.

CHAPTER 2

2.1 The role of psychosocial factors in the pathogenesis of Infectious Mononucleosis

2.2 Introduction

This chapter considers the role of psychosocial factors in the progression of glandular fever (i.e. Infectious Mononucleosis, IM), in particular it aims to compare glandular fever sufferers on a range of physical and psychological measures with a healthy control group and then to compare those in the acute stages of the illness (i.e. those recently diagnosed) with those who have failed to recover from the acute condition and have suffered from the illness for three months or longer.

The first section of this chapter provides an overview of the relevant literature describing the virus, the characteristics of those who tend to develop this disease and the immunosuppressive effects of this virus. This provides a rationale for the sample selected and for further consideration of the recurrence of other infectious illness in this disease. Many of the studies reviewed pay insufficient, if any, attention to the role of health, lifestyle and/or health risk behaviours such as smoking, alcohol consumption and diet. These health behaviours have important implications in research considering health or disease associated with immunosuppressive illness because these behaviours may have a direct effect on the functioning of the immune system. Another important methodological issue is the essential use of a control group, and the need to ensure that differences between the control group and the glandular fever groups are not contaminated by differences in lifestyle and/or health risk behaviours. This study ensured that the participants in the control group and the illness group were matched on important lifestyle and health risk variables.

The second section of this chapter aims to provide a clinical picture of the disease. It gives a description of the main symptoms of the disease as well as

considering issues associated with diagnosis and treatment of this illness. This description of the clinical features of IM enables comparisons to be made between (a) how the illness is described in the literature (b) how the sample used in this study describe their illness. Although a number of studies have described the major symptoms and psychosocial after-effects of IM, there is little detailed information regarding the subjective experience of this illness. This study attempts to provide a more detailed overview of the subjective experience of glandular fever and its impact on psychological well being, behaviour and quality of life.

The third section of this chapter summarises the literature on the relationship between chronic IM and Chronic Fatigue Syndrome (CFS); this is an issue which will be the subject of discussion in the final study in this thesis. It is considered briefly in this chapter because of the overlap between the symptoms experienced by those who fail to recover from IM and the symptoms experienced by sufferers of CFS. The question regarding the role of Epstein Barr virus in the development of CFS is also raised here, highlighting the current controversies surrounding this issue. Recent evidence providing support for a fatigue syndrome following IM is outlined.

These first three sections attempt to provide information relevant to the study of Infectious Mononucleosis. The next two sections provide a more formal review of the relevant literature on the relationship between psychosocial factors and IM.

In the fourth section, the evidence from studies investigating the physical and psychological after-effects of IM is reviewed using a chronological approach. Some of the methodological problems associated with this research are highlighted as well as the need to develop an understanding of physical and psychological problems at different stages of the illness, and in particular in those who fail to recover from the acute condition.

The fifth and final section in this chapter considers research on the role of psychosocial factors in the onset and reactivation of IM, in particular the role of psychosocial factors and stress.

2.3 Characteristics of IM

The Epstein-Barr virus (EBV) is a human herpes virus and is the sole viral agent implicated in the aetiology of IM (Henle & Henle, 1981). IM is primarily a disease of young adults. Age influences the severity of the disease since the viral infection occurs mostly in children where it is asymptomatic. Primary infection can occur later when it emerges as a clinical illness especially in the 15-25 year age group. Among adolescents from upper social classes approximately 25% have the antibody (Kasl, Evans, and Neiderman, 1979) and beyond the late twenties about 95% of the population have been in contact with the disease. The disease is commonly seen in university students in greater incidence than the general population (i.e. the estimated prevalence is between 45-200 per 100,000 in the general population but for college students this rises to between 150-250 per 100,000) and represents the fifth commonest infectious disease in this group (Evans, 1978). Niederman, Evans and Subrahmanyan (1970), in a study of 150 Yale University students, found that only one third carried the antibody to EBV on entrance to college, a further one third seroconverted during the next five years (of whom 28 experienced clinical IM, compared with 15 with no symptoms of the illness).

Saliva is the main route of transfer, although people living in the same house have only a 10% incidence of acquiring IM (Hendler, 1987). It is rare to acquire the infection through a shared drinking glass. IM is commonly referred to as 'Glandular Fever' due to the main presenting symptoms of the disorder being a sore throat and swollen lymph glands.

A variety of antibodies are produced at different stages of infection. After acute infection the virus remains in a latent state within the host B-cells and salivary glands. (Wessely, Hotopf and Sharpe, 1999). The EBV can remain locked away for long periods without alerting the immune system and has the

capability for being reactivated at any time. Reactivation of EBV is well established in some serious immunocompromising diseases such as in AIDS and organ transplant (Randhawa et al., 2000).

Not only is EBV more active in immunocompromised individuals but initial infection leading to IM also has an immunosuppresive effect in itself (Henle & Henle, 1981). This general immunosuppression is experienced for a period of time after IM and may cause greater susceptibility to other viral infections such as the common cold. Previously healthy individuals may be vulnerable to infections for several months following the initial infection and the impact of IM often extends well beyond the symptomatic acute phase. (Smith, Thomas, Borysiewicz and Llewelyn 1999).

2.4 Clinical picture of IM

The main symptoms of IM include a sore throat and swollen lymph glands, a high temperature, headache and fatigue. The illness lasts, on average, from 4-6 weeks with 1-2 month incubation and a prodrome of 2 weeks where mild respiratory symptoms are experienced.

Young adults are generally moderately ill and confined to bed for 5-10 days and normally return to full activity in 4-5 weeks although it is not uncommon for the illness to persist for much longer, with many experiencing delayed recovery and ongoing relapses. In persistent cases the major symptoms are fatigue, depression and general lethargy. There appears to be a wide variation in the duration and severity of this disease. Buschwald et al. (2000) investigated recovery from IM in 150 patients. At two months, 38% (N=55) had failed to recover from the illness and at 6 months follow up 12% (N=17) had still not fully recovered. This confirms the limited information on recovery from IM which indicates that the majority of those suffering from acute IM recover spontaneously within 4 weeks but that a significant minority fail to recover and develop what has been referred to as 'chronic mononucleosis' or other prolonged states of illness. (e.g. Straus, 1985; Borysiewicz, 1986).

2.5 Blood tests in acute IM

The clinical features of IM are not easily differentiated from infection by other common infectious diseases so a confirmatory blood test is usual. A blood film showing 10-15% atypical lymphocytes (with enlarged nuclei) plus a positive Paul-Bunnell test normally identifies the illness in a patient falling into the appropriate age range. The Paul-Bunnell test makes use of the initial non-specific antibody response made by the B-cells. Such heterophile antibodies rise in parallel with EBV specific antibodies. The test employs an agglutination reaction of the antibodies with sheep red blood cells (Paul & Bunnell, 1932). A slightly less accurate variation known as the 'monospot' test based on horse cells is also in regular use. The advantage of the heterophile test over EBV specific tests is that it is cheap, rapid and reliable, being positive for around 90% of patients who are experiencing symptoms of IM for the first time (Smith, 1991). It becomes positive in the second week of the illness and may remain so for several weeks although this varies between individuals. The Paul Bunnell test cannot demonstrate reactivation of the illness and this is when specific antibody responses become more important (see below).

2.6 Treatment of IM

There are few treatments for IM; Acyclovir is used in herpes zoster and herpes simplex infection where it successfully inhibits DNA synthesis in viral replication however it only works in active replication (Hirsch & Kaplan, 1987). Yao and colleagues (1989) found that in acute IM the drug reduced viral shedding from the throat but did not change the number of virus infected B-cells. The value of Acyclovir in IM is disputed (Anderson & Ernberg, 1988, Van der Horst et al., 1991) and it is not normally prescribed. Steroids are sometimes used for symptomatic relief and antibiotics are given to deal with secondary bacterial throat infections. There are no vaccines available to prevent the development of clinical IM. This lack of medication means there are no methods of preventing either onset nor reactivation of EBV.

2.7 Chronic IM and CFS

A relatively new clinical syndrome described as chronic IM was more recently identified. A paper in the Lancet in 1982 by Tobi, Morag and Ravid, reported evidence for a prolonged illness associated with serological evidence of persistent EBV infection. This research was followed by two papers by Jones and colleagues (1985) and Straus and colleagues (1985) describing a similar association. The notion of 'chronic active EBV' expanded rapidly and became strongly associated with chronic fatigue and subsequently CFS. The link between EBV and CFS gained support, however after a relatively short time subsequent investigations started to cast doubt upon this link. For example, Holmes, Kaplan, Stewart, Hunt, Pinksky & Schonberger (1987) in a case-control study of individuals from the Lake Tahoe epidemic found elevated antibodies not just to EBV but also to cytomegalovirus, herpes simplex and measles, although this was not confirmed by others. Buchwald, Sullivan & Komaroff (1987) pointed out the importance of selection factors in the original reports; many patients had been referred on the basis of their abnormal serological responses to EBV. By the end of the 1980s, opinion was moving away from the etiologic role of EBV in the pathogenesis of CFS (Straus, 1988; Swartz, 1988).

More recently, however, a number of studies, have reported renewed evidence for the role of EBV in CFS.

Jones and colleagues (1991) investigated the EBV immune response and molecular epidemiology, specifically the differential responses of B-lymphocytes to experimental manipulation. Using a variety of healthy controls, based on their record of previous IM and serological evidence of exposure to EBV, they were able to induce B-cell transformation, indicating active infection, in about 30 percent of CFS cases showing the early antigen, compared to between 5-10 percent of the controls. When considering the characteristics of the viruses involved, they were unable to find substantial differences in the strains of the virus between cases and controls, which implied that any deficit might be host rather than virus related. Whilst they do

not claim to have demonstrated that EBV is a causative agent in CFS, they suggest that in a subset of CFS patients the host immunological surveillance system that suppresses circulating EBV-transformed cells may be diminished, permitting reactivation of the virus.

More recent support for a fatigue syndrome following EBV infection comes from research carried out by White, Thomas, Amess & Grover (1995). In this prospective cohort study, White and colleagues compared patients with either IM or an upper respiratory tract infection (URTI) and found evidence for the existence of a fatigue syndrome after IM. The precise figures for a fatigue syndrome following both glandular fever and other similar viral infections are shown in the table below.

Table 2: The prevalence of a fatigue syndrome after viral infection

	Onset	2 months	6 months
Glandular Fever (n = 108)	58%	41%	10%
Glandular fever-like illnesses (n = 83)	44%	18%	4%
Upper respiratory tract infection (n=54)	24%	4%	0%

(adapted from White, 1995)

The fatigue syndrome described by White et al. consisted of the following symptoms: (a) physical and mental fatigue, (b) retardation, (c) hypersomnia and poor concentration, (d) psychomotor retardation, (e) irritability, (f) social withdrawal, (g) emotional lability, and (h) a transient sore throat and neck gland swelling with pain. Fatigue at 2 months was associated with the severity of the illness but at 6 months it was not associated with any physical factor apart from lack of physical fitness at 2 months. CFS was predicted by a positive monospot test and lower physical fitness but this depended upon the definition of CFS used. Both mood disorder at 2 months and emotional

personality predicted the Oxford-defined CFS.[1] They suggest that psychosocial factors are unimportant in a fatigue syndrome of several months duration but may become more important with time.

Depression was associated with pre-morbid psychiatric history, an emotional personality and concurrent life events. White et al. draw a distinction between depression and fatigue at 6 months and suggests that these have different triggering factors. They suggest that the strongest predictor for mood disorder following glandular fever is pre-morbid psychiatric disorder, social adversity and emotional personality.

2.8 Psychological and physical after effects of EBV infection

Despite the fact that it was not until the mid 1980s until the notion of a chronic condition following EBV was suggested, there was some speculation regarding prolonged states of anxiety, depression and fatigue following the infection prior to this.

In 1959, Greenfield, Roesler and Crosley argued that recovery from IM was delayed in those with 'weaker ego strength'. They argued that it was this, rather than the illness itself, which was associated with post illness depression. This study had the substantial methodological weakness that the psychological characteristics were assessed following the illness and may therefore have been contaminated by the illness itself.

Cadie, Nye and Storey (1976) reported on thirty six patients with IM who were followed up one year after their diagnosis. They used the Middlesex Hospital Questionnaire (measuring anxiety, phobia, obsessionality, somaticism, depression and hysteria) and a structured interview to investigate the presence of psychiatric symptoms before and after IM. They concluded that IM leads to depression in a number of cases but in this study only women appeared to be affected. Again there were methodological weaknesses due to

[1] There are two main criteria for the definition and diagnosis of CFS. This is the Oxford criteria and the C.D.C. criteria. These are outlined and explained in Chapter 8. p.180

retrospective reporting of psychiatric symptoms which were measured one year after the diagnoses.

Hall and Smith (1995) describes increased depression, anxiety and obsessive symptoms following IM, with few differences between those in the acute phase and those who had been diagnosed with the illness 6 months prior to testing. They found specific effects of IM on measures of mental performance with differences between those in the early stages of the illness (i.e. less than two months since diagnosis - acute group) and those who had been diagnosed at least six months prior to testing (i.e. chronic group). Those in the acute phase of the illness were significantly slower than controls on simple reaction time and a sustained attention test. Those in the chronic phase of the illness were significantly worse than controls on recalling words from a list (i.e. a memory task) and were less accurate on a logical reasoning task. The effects observed in the chronic group were similar to those observed in studies of CFS patients, although there was no evidence of psychomotor slowing in the CFS group which generally there is. Perhaps surprisingly there were few differences between those in the acute phase and those in the chronic phase of the illness in terms of symptoms, with significant numbers of the chronically ill still reporting the major symptoms of the illness - sore throats and swollen glands, although there was a slight reduction in symptom severity. Higher levels of depression and anxiety were reported in both acute and chronic IM groups compared with controls.

Further to the earlier report of fatigue following IM, White and colleagues (1998) calculated what they describe as a conservative estimation of the general population risk of CFS following IM. They state that given the average incidence of IM of 69.1 cases per 100,000 population (based upon 1993-1995 data from the Communicable Disease Surveillance Centre), which is probably an underestimation as many cases go unreported or undiagnosed, that IM precipitates 3113 cases of Centre for Disease Control (CDC) criteria CFS in England and Wales per annum (NB: there was a greater prevalence of CFS using the Oxford criteria compared with other criteria, including the CDC criteria).

White et al (1998) also reported on the incidence of psychiatric disorders following glandular fever. The prevalence of all psychiatric disorders, in all groups (IM and other URTI) was 29% in the fortnight before onset (based on retrospective reports). The numbers suffering from a psychiatric disorder at the onset of their infectious illness rose to 55%, however those suffering fro a psychiatric illness six months after diagnosis was not significantly higher than controls.

Major depressive disorder was found to occur in 28% of patients with EBV, 14% of non EBV glandular fever patients, and only 11% of URTI patients. Major depressive disorders lasted between 2-5 weeks after infectious illness onset. Generalised anxiety disorder rose from 1% prior to onset, to 6% at onset and was identified in 4% of cases by six months.

White and colleagues reported a 90% increase in psychiatric morbidity at onset, mainly for mood disorders, but no significant differences after six months. They suggest that post infectious fatigue was largely independent of psychiatric disorders in the first few months after the onset of infection but that psychiatric disorder become an important factor in those still fatigued at six months. This suggests that it was the fatigue triggering the psychiatric disorders rather than the psychiatric disorders triggering the fatigue.

Jones (1994) found that at 2 months and 6 months after onset of IM there were highly significant positive associations between provoking agents (i.e. severe events and major difficulties unrelated to infection) or significant stressors and the presence of a psychiatric disorder. The association with depressive illness alone was even more significant and appeared to be greater at 6 months than at 2 months. This association was not present at the onset of infection suggesting that 'social adversity' may be an important factor for psychiatric disorders, especially depressive illness following acute infections. Jones found little association with the development of post-infectious fatigue syndrome or delayed physical recovery.

Katon, Russo, Ashley and Buchwald (1999) studied the prevalence of psychiatric disorders and psychological distress in those with acute IM and over the subsequent six months of the illness. They found that psychological distress was high during the acute stages of illness however few met the full criteria for psychiatric illness as found in the Diagnostic and Statistical Manual (DSM-III-R). Increased psychological distress at 2 months was associated with (a) lower social functioning in the month prior to diagnosis, (b) higher aspartate aminotransferase levels, (c) less confidence in the physician and health care system (i.e. locus of control), and (d) less severe physical symptoms at baseline. Greater distress at six months was associated with an increased number of adverse life events in the six months after developing IM and more days of reduced activity in the 2 weeks prior to the onset of IM. Both biological and psychosocial factors were related to psychosocial distress at 2 months whereas psychosocial factors were more important at 6-month follow up. In this study, however, they used only patients who were seeking health care and there was no control group.

Until these more recent studies, there was little reliable evidence concerning the precise psychological sequelae of IM, only speculation based on clinical observations. IM appears to be a relatively common and debilitating illness and there remains to be only limited information concerning its progression and in particular the reasons for delayed recovery from the illness and the role of psychological stress. There continues to be uncertainty and disagreement regarding the role of psychosocial factors in IM, and there is a need to elucidate more precisely the psychological and psychosocial morbidity prior to, during, and following IM as well as the existence and severity of symptoms in the acute phases of the illness and in the progression of this disorder. In particular, there is a need to understand the pathogenesis of the disease in people who do not appear to recover appropriately after the initial infection.

2.9 Role of psychosocial factors in the onset, reactivation and severity of EBV

There is some evidence which suggests that initial susceptibility to EBV is enhanced by certain psychosocial stressors. Kasl, Evans and Niederman (1979) carried out a prospective study of IM over 4 years in one class of 1,400 cadets at the West Point Military Academy. Upon entry about one third of the cadets lacked the EBV antibody and 20% of these became infected (i.e.seroconverted). About one quarter of those who became infected developed definite and clinically recognised IM. Certain psychosocial risk factors were associated with the development of clinical IM:

1. Having fathers who were "overachievers"
2. Having high levels of motivation
3. Doing relatively poorly academically

This combination of high motivation and poor academic performance interacted in predicting clinical IM. Furthermore, the same set of psychosocial risk factors were also associated with elevated EBV antibody titers among individuals who seroconverted without apparent clinical symptoms.

Glaser and colleagues (1985b) investigated changes in antibody titers to three latent herpes viruses (EBV, cytomegalovirus and HSV) associated with academic stress. Three blood samples were taken from 49 medical students on the following occasions: (a) one month before final examinations, (b) on the first day of the examinations, and finally (c) during the first week after their return from summer holidays. The antibody titers to all three herpes viruses changed significantly across the sample points with the lowest levels found at the third point (i.e. after the holidays) where students were least distressed. They also found that lonelier students had significantly higher antibody titers to two different EBV antigens compared with their classmates who described themselves as less lonely on the UCLA Loneliness Scale

To test the specificity of these changes for herpes virus latency, rather than more global antibody changes, antibody to poliovirus type II was also measured (NB: most students would have the antibody due to widespread school vaccination programs). Significant changes in poliovirus antibody titers were not found which suggested that the changes in herpes virus antibody titers observed in latently infected individuals reflected specific stress-related modulation of virus latency. It is possible that pre-existing stress, or stress associated with the illness itself, could exacerbate the clinical symptoms and possibly affect the course of the illness.

This review of the literature suggests that psychological distress and depression commonly follow an infection with Epstein Barr virus and that in some individuals, prolonged fatigue occurs following the initial infection and may persist. Further investigation of the precise psychological and physical effects of this illness as well as their role in the progression of the illness in those who fail to recover from the initial infection is justified. This study aimed to investigate a range of psychological and physical consequences of this illness as well as comparing those with a chronic illness (who had failed to recover from the acute illness) with those who had been recently diagnosed (acute). The study aimed to overcome some of the methodological difficulties described earlier, in particular controlling for negative affect and health risk behaviours. The full aims and objectives of this investigation of Infectious Mononucleosis are set out below :-

2.10 Aims of this study

The overall aims of this study were to investigate the pathogenesis of IM as follows:

1. To achieve a clearer understanding of the natural history of the disorder and its progression by investigating psychosocial and physical precursors to the disorder, as well as psychological and physical effects and after effects of the disorder

2. To compare the control group and the IM groups on other medical, lifestyle and health risk behaviours
3. To provide a more detailed description of the subjective experience of those suffering from this disease as well as their perceptions of the impact of the disease on their life and relationships
4. To describe the clinical picture of the disorder at different stages of the illness and to investigate recurrence of other infectious illness in IM patients compared with controls
5. To investigate psychological characteristics of sufferers at different stages of the illness and to compare those in the acute and chronic stages of the illness and to compare chronic IM patients with the acute symptoms with those not suffering the acute symptoms
6. To achieve a clearer picture of both the immediate physical and psychological effects and longer term effects of this disorder, in particular perceived stress, negative mood, depression and anxiety
7. To describe the clinical and psychosocial characteristics of those who fail to recover from the acute illness

The next chapter describes the cross sectional study of Infectious Mononucleosis, outlining the methodology and measures used to compare those in the acute stages of the illness with those who were suffering a form of chronic illness (i.e. they had not recovered from the initial acute infection and continued to experience the symptoms of IM).

CHAPTER 3

3.1 Study One: A Cross Sectional Study Of IM

The first study of glandular fever was a cross-sectional investigation of differences between those in the acute stages of the illness, those who were suffering from chronic IM (i.e. still suffering symptoms but had been diagnosed with the illness at least six months before) and a control group who had not suffered from the illness.

3.2 Methodology

3.2.1 Design

This was a cross-sectional study of the difference between participants suffering from IM and a control group of healthy participants. This study was also designed to evaluate differences between those defined as acute IM sufferers and chronic IM sufferers. It also considered differences between chronic IM participants with the acute symptoms and those not suffering the acute symptoms at the time of study, but who had not recovered fully from the illness. This was a between-subjects design with a control group matched with the experimental group for relevant, potentially confounding variables.

The analyses in this study were conducted using BMDP statistical package The analyses include a number of specific statistical tests including: t-tests, Analysis of Variance (ANOVAs), Analysis of Co-variance (ANCOVAs), as well as correlations and partial correlations. In a small number of analyses, where data was categorical, both Chi Square and Anovas were conducted. Because of the problem of small samples leading to very low frequencies in some cells and because the results of the analyses were the same for both Anovas and Chi Square, most of the analyses in these studies relied upon Anovas.

3.2.2 Participants

Much of the research in this area is undertaken at hospitals and clinics. This makes the recruitment of participants easier and allows easier access to large numbers of participants with the relevant illnesses. Research using only participants attending clinics has the drawback of a potential bias in the sample recruited. A number of studies have referred to the need to recruit participants from the general population and not restrict samples to only those attending clinics. Characteristics of those attending clinics may be that they firstly are at the more severe end of the spectrum of symptoms, therefore more likely to seek help, and secondly that they actually choose to seek help (even though there is little in the way of treatment for viral illness of this kind).

This study is based on recruitment from the general population and the analyses, whilst considering a range of important variables, looks at the levels of these variables across different groups and/or categories. The potential for confounding variables was controlled using ANCOVA and partial correlations.

In the introduction it was noted that young adults, and in particular university students, have a higher incidence of clinically manifested IM and it was decided therefore to use a sample of university students in this study. In order to obtain a broader spread of demographics, three universities were selected for inclusion in this study, two in South Wales (one 'new university' and one 'traditional') and one in Bristol (another 'traditional university').

Participants were recruited via a poster campaign at these three locations: University of Bristol, University of Cardiff and University of Glamorgan. Posters advertised for people who were currently suffering from IM (though on the poster the term 'glandular fever' was used) or who had been diagnosed with IM in the past 12 months. (Appendix A1.1). The table below shows the number of participants recruited at each of the three locations, Cardiff, Glamorgan and Bristol. (Appendix A3.1).

Table 3: Location of Recruitment of Participants for the Glandular Fever Study

Location	No. of Participants
Cardiff	9
Glamorgan	27
Bristol	38
Total	74

Upon recruitment Participants were given some information about the study and the procedures. They were asked to complete the following forms (see Appendix A1.2 and A1.3):-

1. Glandular Fever information sheet to provide information about their diagnosis, their General Practitioner (GP) and contact details
2. Consent form in order to obtain confirmation of the diagnosis from their GP

Upon completion of these, a letter and a brief questionnaire requesting information regarding their diagnosis and blood test was sent to their GP (see Appendix A1.5, A1.6 and A1.7).

A sample of healthy recruits who had not suffered from IM was also recruited at these universities, to act as a control group. Recruitment methods are explained more fully in the paragraph which outlines the procedure.

Of the 74 participants, 6 did not return booklets and were not included in the study. The total number of IM participants included in the first analysis was 68. Of the 68 IM participants, 13 indicated that they had recovered leaving a total of 55 participants; the 13 recovered participants were analysed separately. The table below shows the number of participants broken down by age, gender and location. This sample size is relatively small compared

with the more recent investigations of psychosocial factors in IM. Katon (1999) for example started with 797 participants and ended up with 333 participants who met the criteria. This study, however, was set in a large health maintenance organisation in the U.S.A. that provided prepaid health care through two hospitals and 23 outpatient clinics. The main study in the U.K., by White et al. included 245 participants in a primary care setting. 44% (108) of these had confirmed or probable primary EBV infections. An important distinction between these studies and the current study, however, is the fact that participants for this study were a 'community sample' rather than a sample of patients attending clinics or hospitals. This has the advantage of avoiding the bias associated with only using those attending clinics – who are likely to have more severe symptoms than a community sample. The sample size, as a consequence of greater difficulties recruiting participants, however is significantly smaller.

Table 4: Number, Gender, Age and Location of the Participants in the study

Participants	Total	Gender	Age	Location
Glandular Fever	55	Male 18(33%) Female 37(67%)	mean=20.8 mode=19 range 18-40	Bristol 27 (49%) Glam 22 (40%) Cardiff 6 (11%)
Healthy Controls.	82	Male 30 (37%) Female 52(63%)	mean=21.8 mode=19 range 18-42	Bristol 36 (42%) Glam 46 (58%) Cardiff 0
Recovered	13	Male 8 (62%) Female 5 (38%)	mean=19.6 mode=19 range 18-23	Bristol 10 (76%) Cardiff 3 (24%) Glam 0

3.2.3 Procedure

Participants were recruited via posters and were given the conditions for participating in the study together with a brief explanation of what was involved. At this stage in the procedure inclusion criteria were fairly broad. Participants were included in the study if they confirmed that they were either currently suffering from a recurrence of IM *or* had been diagnosed with IM within the past 12 months. It was emphasised that diagnoses must be confirmed by a blood test and that GPs would be contacted to obtain such confirmation. Participants not conforming to these conditions were excluded at this stage, however actual confirmation was not obtained until after participation as it often took some time for GPs to respond. Stricter inclusion criteria were later considered and this is described in a later section. After they had agreed to participate, an appointment was made for participants to return to the laboratory for tests. At this time they were given written information about the study and were asked to complete a booklet containing questionnaires and to bring the completed booklet back with them when they returned for testing. The booklet took approximately 20 minutes to complete. Participants were allocated a number and were assured of confidentiality.

3.2.4 Measures and materials

As well as demographic information about the participant and information regarding their medical history and health behaviours (Appendix A2.1), the instruments were selected in the areas discussed earlier:

1. Measures of psychological stress.
2. Coping strategies and social support.
3. Mood and depression
4. Personality characteristics
5. Outcome measures

Appropriate measures were selected within these domains on the basis of an evaluation of their use in previous research and their reliability and validity in

measuring the relevant variables. The justification for the selection of variables was discussed in the introduction and on this basis a range of measures were included.

3.2.5 The questionnaire

The questionnaire (see Appendix A2.1) comprised four main sections:

Section 1: addressed socio-demographic factors including age, gender, marital status, education and employment; questions about their general medical history including current health status, allergies, previous illness, medication use and the occurrence of other infections diseases; IM participants were required to provide information regarding their diagnosis and symptoms in the early stages of the illness. (Appendix A2.3).

Section 2: addressed lifestyle factors and health related behaviours and included questions on sleep, diet, smoking, alcohol consumption and exercise

Section 3: addressed the IM participants only and considered details of their illness: current health status and illness severity; changes in susceptibility to other infectious illness; changes in health and behaviour since the onset of IM; behaviour which improved feelings of well being and behaviour which exacerbated feelings of illness; incidence and level of recurrence of IM; progression of the illness; and the impact of illness on work, social relations and general functioning

Section 4: comprised a battery of paper and pencil standardised tests designed to measure variables relevant to the conceptualisation of stress described earlier. This section was given to all participants. The following scales were included:

3.3 Measures of objective and subjective stress

3.3.1 The Life Events Scale (Appendix A2.4)

This was developed by Henderson, Byrne and Duncan-Jones (1981) and adapted by Cohen, Tyrell and Smith (1991) who reduced the original 67 item list of recent events to 23 items. It measures not only the occurrence of major life events (both positive and negative) in the past twelve months but also their impact (i.e. whether it was a good or bad experience); this is an improvement on many of the previous 'life events' scales such as Holmes and Rahe (1967) because it measures positive and negative life events and also takes into consideration the impact of those events. This provided a more 'objective' measure of stress in terms of the negative events actually experienced by participants in the past twelve months. It also allowed participants to 'add' their own events to the list if they felt they had experienced an important event which had not been included in the list but which they felt had had an impact on their life. The variables derived from this scale were: a. Positive Life Events b. Negative Life Events and c. Total Life Events.

3.3.2 The Daily Hassles Scale (Appendix A2.5)

It has been established that, as well as major life events, daily hassles in the form of irritating and frustrating background stressors are also important sources of stress, particularly when they accumulate (e.g. Weinberger et al., 1987). The Daily Hassles Scale has been widely used in stress research and measures the frequency, cumulative severity and intensity of daily hassles. The scale was developed by Kanner, Coyne, Schaefer and Lazarus (1981). It consists of 117 hassles involving work, health, family, friends, environment, practical considerations and chance occurrences. Summary scores on the hassles scale incorporate: (a) a simple frequency count; (b) cumulative severity, (c) the sum of the three point severity ratings and (d) the intensity (i.e. the cumulated severity divided by the frequency).

3.3.3 The Perceived Stress Scale (Appendix A2.6)

This is a global measure of perceived stress developed by Cohen, Kamarck and Mermelstein (1983) and was designed to measure the degree to which situations in one's life are appraised as stressful. The importance of cognitive appraisal in the experience of stress indicates the need for measuring the perception of stress as well as the more objective occurrence of stressful events. The Perceived Stress Scale is a 14-item measure of the degree to which respondents find situations in their lives unpredictable, uncontrollable and overloading. These three issues have been found to be central to the experience of stress (e.g. Lazarus, 1977; Seligman 1975). The scale also includes a number of direct queries about current levels of experienced stress.

3.4 Measures of personality and disposition

3.4.1 Dispositional Optimism (LOT) (Carver & Scheir, 1987) (Appendix A2.7)

This short, 12-item scale asks respondents to indicate on a four-point, likert type scale the extent to which they agree with a range of statements reflecting optimism or pessimism. Dispositional optimism has been associated with positive health outcomes and is a personality characteristic which may be associated with stress and illness relationship either directly or indirectly.

3.4.2 Trait Anxiety (Spielberger et al., 1970) (Appendix A2.8)

This 20-item scale measures general, stable proneness towards responding anxiously to stressful situations. This is one of the most widely used measures of anxiety in psychological and clinical research (Bowling 1995). This scale is used as a measure of negative affectivity. The alpha coefficient is high (r=0.90) indicating internal consistency. Test-retest correlations with college students showed stability (0.65-0.86).

3.4.3 Multidimensional Health Locus of Control Scale (Wallston et al., 1976; 1978) (Appendix A2.9)

Health locus of control refers to the perceived control a person feels that they have over their health. The later version used here measures three dimensions of health locus of control beliefs, namely (a) internal, (b) powerful others and (c) chance externality. Wallston et al (1978) reported internal consistency alphas of (0.40-0.72) and test-retest correlations of 0.58. Correlations in the expected direction with health status supported the construct validity of the scale.

3.4.4 Self-Esteem Scale (adapted from Fleming & Watts, 1980) (Appendix A2.10)

Self esteem is an important personality construct which may impact coping strategies and should be included in any measurement of stress. Cohen, Tyrell and Smith (1991) adapted the Feelings of Inadequacy Scale and developed the 14 item version used in this study.

3.5 Variables associated with Secondary Appraisal

3.5.1 The Ways of Coping Questionnaire (Folkman & Lazarus, 1980; 1988; 1988) (Appendix A2.11)

This scale assesses how people cope with the stresses of everyday life and is based directly on the cognitive transactional theory of stress. Respondents are asked to identify a specific stressful situation and rate on a four-point scale their reliance on the specific coping responses. Responses can be categorised into the following 6 strategies: (a) problem solving, (b) confrontative coping, (c) positive readjustment, (d) seeking social support, (e) escape-avoidance, and (f) distancing. Folman and Lazarus (1980) report high levels of inter

rater reliability (91%) The internal consistency co-efficients (Cronbach's alpha) were 0.80 and 0.81.

3.5.2 The Interpersonal Support Evaluation List (ISEL) is a Social Support Scale (Cohen & Hoberman, 1983) (Appendix A2.12)

This is a 40 item measure of stress responsive support resources with sub scales of appraisal, belonging, self-esteem and tangible support. ISEL was designed to assess the perceived availabilityh of four separate functions of social support. Scores were calculated for each of the four sub scales as well as a total score which is the sum of the sub scales. Support may act as a buffer against the effect of stressful events or lack of support can be a source of stress in itself. The internal reliability (Cronbach's Alpha) for the total ISEL scale is .77 and the subscales range from .60 to .77. (Cohen & Hoberman 1983)

3.6 Measurements of physical and mental health

3.6.1 The Profile of Fatigue Related Symptoms (Ray et al., 1992) (Appendix A2.13)

This 54-item measures the experience of physical and psychological symptoms in the past week. Responses are scored according to the following four categories: (a) cognitive difficulty, (b) somatic symptoms, (c) fatigue, and (d) emotional distress.

3.6.2 The Beck Depression Inventory (Beck et al., 1961) (BDI) (Appendix A2.14)

This 21-item inventory measures cognitive and physical symptoms of depression in the form of statements ranked in order of severity. The scale has been widely used and correlates highly with psychiatrist's ratings of depression (Beck et al., 1988). The BDI correlates with other depression scales as well as Psychiatrists assessments, (0.66 and 0.75)(Beck 1970). A review of the literature by Beck et al (1988) showed concurrent validity to be

high (0.70 for psychiatric patients and 0.74 for non psychiatric patients. Beck also reported split half reliability was r=0.86 and test re-test correlations of above 0.90.

3.6.3 The Positive and Negative Mood Scale (Zevon & Tellegen, 1982) (Appendix A2.15)

This 65-item adjective checklist measures mood by a list of adjectives, not symptoms (which could reflect physical problems). The shortened version, used in this study contains 30 items – 15 measuring negative mood and 15 measuring positive mood. Respondents are required to indicate the extent to which they have experienced that mood state during the past week on a 5 point scale from 0 (not at all) to 4 (very much so).

The results of this study are presented in the next chapter.

CHAPTER 4

The previous chapter outlined the methodology for this study and the measures which will be used in this study and in subsequent studies in this thesis. This Chapter presents the results of the analysis of the Glandular Fever Study.

4.1 Glandular Fever Results One

The results of the glandular fever analysis are presented in four sections; the information presented in each of these four sections is described below.

4.1.2. Section One

Section one aims to provide a detailed description of the characteristics of the illness as perceived by those suffering from glandular fever. It includes their perception of their current illness status and the impact the illness has had on specific aspects of their life. Whilst there is some information regarding the clinical progression of glandular fever few studies have investigated both the physiological and psychological effects of this illness in any detail, especially the specific effects of the illness on lifestyle and behaviour. Neither is there much information regarding the sufferers' perceptions of the progression of their illness and their experience of factors that lead to an improvement or deterioration in their condition. This section aims to give an overall picture of the progression of this illness as experienced by those suffering from it.

In section one the overall characteristics of those suffering from glandular fever were reported providing information on their perceived illness status and the relationship between illness status and psychological stress, depression and emotional well being. The symptoms experienced at diagnosis are reported and their current understanding of factors that influence their health and recovery. Finally, participants' perceptions of the trajectory of their illness progression is reported.

4.1.3. Section Two

This section considers comparisons between the glandular fever group overall and the (healthy) control group on demographic variables, general health and health behaviour. This was to ensure that the groups were matched on these variables and that further analyses were not confounded by other difference between the groups that might influence the results. It is well established that socio-demographic factors can influence health outcomes as can lifestyle factors such as diet, exercise and smoking. Differences between the groups on these variables could account for differences in health outcomes and it was therefore important to ensure that the groups were matched on these factors. Differences between the glandular fever group and the control group in symptoms currently experienced were reported in this section and any differences between participants from different locations were also considered. This section aims to ensure that the glandular fever participants in this study demonstrate the classic characteristics of the illness and that subsequent analysis of differences between the control group and the glandular fever groups are not confounded by variables, other than the illness, which might account for differences between the groups.

4.1.4. Section Three

This section considered differences between the glandular fever group and the control group on measures of objective and subjective stress, mood, disposition, fatigue-related symptoms, coping strategies and social support. These analyses aimed to demonstrate *anticipated* differences between the illness and control groups on stress and other psychosocial variables before going on to consider the differences between sub categories of glandular fever.

4.1.5. Section Four

This fourth and final section considered differences between the groups at different stages of the illness, in particular those in acute and chronic stages of the illness were compared and each of these groups was compared with the

control group. The issue of categorisation or case definition was considered here (i.e. what should the cut-off points should be for the acute and chronic definitions and how this might influence the analysis.). Appropriate case definitions were then identified for comparisons between the groups to be made. The following questions were addressed in this analysis:-

1. Are symptoms the same or different in the chronic group compared with the acute group and what is the nature of these symptoms? Do those in the chronic stages of the illness continue to experience the classic acute symptoms of glandular fever (e.g. sore throat, swollen glands, and high temperature) or are these replaced by another set of symptoms?

Does fatigue continue to be a major physical problem in the chronic stages of the illness and does the experience of fatigue get worse, better or remain unchanged?

2. What are the differences between these groups in susceptibility to other infectious illness, including colds and upper respiratory tract infections?
3. What are the differences in psychosocial measures?

   3.1 What are the differences between the groups in perceived stress, objective stress and daily hassles? Are there differences in stress between the glandular fever groups and the controls and are there differences between those in the acute and the chronic stages.

   3.2 What are the differences between the groups in mood, depression and personality characteristics including dispositional optimism and self esteem?

   3.3 What are the differences between the groups in psychological and somatic difficulties (cognitive difficulties, emotional difficulties, somatic symptoms and fatigue)?

   3.4 What are the differences between the groups in the effectiveness of managing stress (e.g. coping and social support)?

4. Are any differences between the groups maintained when negative affectivity is controlled?

4.2 Section One

Characteristics Of The Illness As Perceived By Glandular Fever Sufferers

Thirteen participants stated that they were now fully recovered from glandular fever, these participants were removed from the analyses presented here.

4.2.1 Perceived illness status/severity

Those with glandular fever categorised their current state of health in relation to glandular fever as follows: 4% (2) reported that the severity of their illness was currently worse than ever; 5% (3) reported that they were bad; 7%(4); reported that they were bad but recovering; 42% (23) reported that they were recovering with lapses and 42% reported that they were almost recovered. There was no correlation between illness status and illness length (r=0.116).

The glandular fever participants were also asked to report how frequently they suffered recurrences of the illness. 6 (12%) said they were constantly ill; 9 (18%) said that they suffered recurrences at least once a week; 22 (44%) at least once a month; 6 (12%) at least once every six months and 9 (17%) not at all. 75% stated that they suffered recurrences of the illness monthly or more.

In terms of their illness severity over the past month, 21 (40%) said that it was bad; 25 (48%) said that it was an average month and 6 (12%) reported that it had been a good month.

The association between psychosocial measures and illness severity was investigated using analysis of variance (ANOVA). There was a general trend for scores on measures of psychological distress to decrease as severity of the illness decreased. The above responses were collapsed into three categories (i.e. 1=worse than ever or bad; 2 = bad but recovering or recovering with lapses and 3 = almost recovered).

Table 5: Mean Scores (sd) on Psychosocial Measures by Current perceived illness severity where 1= Severely ill and 3=less Severely ill

Illness Severity	Perceived stress Mean (sd)	Depression Mean (sd)	Emotional Difficulty Mean (sd)
1 (Severe) n=5	30.4 (8.9)	13.7 (8.6)	48.4 (24.4)
2 (moderate) n=27	25.8 (4.3)	9.9 (7.1)	41.3 (18.6)
3 (almost rec) n=23	24.5 (5.8)	6.2 (4.9)	32.1 (14.4)

(1=worse than ever or bad; 2 = bad but recovering or recovering with lapses and 3 = almost recovered).

Whilst the differences did not reach significance, the trend was consistently in the direction of higher the mean scores on the psychosocial variable the more severe the current illness.

The next table shows the symptoms experienced by the glandular fever sufferers when they were first diagnosed with the illness. The symptom profile of this group is characteristic of those suffering from this particular illness, with the classic symptoms experienced by this group.

Table 6 : Symptoms most commonly suffered in the *first four weeks* of illness and the numbers of IM sufferers reporting these symptoms

Symptom	No. and Percentage Reporting
Fatigue	52 (98%)
Sore Throat	49 (93%)
Swollen glands	48 (91%)
Physical weakness	47 (88%)
Headache	45 (85%)
Loss of appetite	42 (79%)
Hot/cold spells	38 (72%)

Loss of concentration	38	(71%)
Sweating	35	(66%)
25 (44%) report that they are more susceptible to colds		
Fever	30	(57%)
Muscle aches	30	(57%)
Depression	29	(55%)
Insomnia	27	(51%)
Cough	21	(40%)
Nausea	21	(39%)
Sore eyes	19	(35%)
Anxiety	17	(32%)
Noise sensitivity	16	(30%)
Light sensitivity	14	(26%)
Loss of memory	13	(25%)
Swollen spleen	12	(22%)
Stomach	9	(17%)
Heart racing	6	(11%)

The next series of tables shows the impact of glandular fever on subsequent behaviour and general health.

Table 7: The impact of glandular fever on subsequent behaviour

46 (81%) stated that they need more sleep than before
37 (65%) stated that the quality of their sleep was worse
37 (64%) stated that they take less exercise than before
31 (55%) stated that they drink less alcohol

Table 8: The frequency of other infectious illnesses since diagnosis

14 (23%) report that they are more susceptible to gastrointestinal problems
17 (29%) report that they are more susceptible to fungal infections

Table 9: The factors which lead to an improvement in health include:

Rest	43 (77%)
Sleep	49 (87%)
Eating well	14 (25%)
Vitamin supplements	15 (27%)

Table 10: The factors leading to worsening of health include:

Lack of sleep	49 (87%)
Stress	47 (83%)
Other illness	35 (62%)
Concentrating	34 (60%)
Exercise	25 (48%)
Alcohol	18 (31%)
Shopping	17 (29%)
Walking	12 (23%)
Reading	12 (23%)

4.2.2 Summary of the Impact of the Illness on behaviour and health

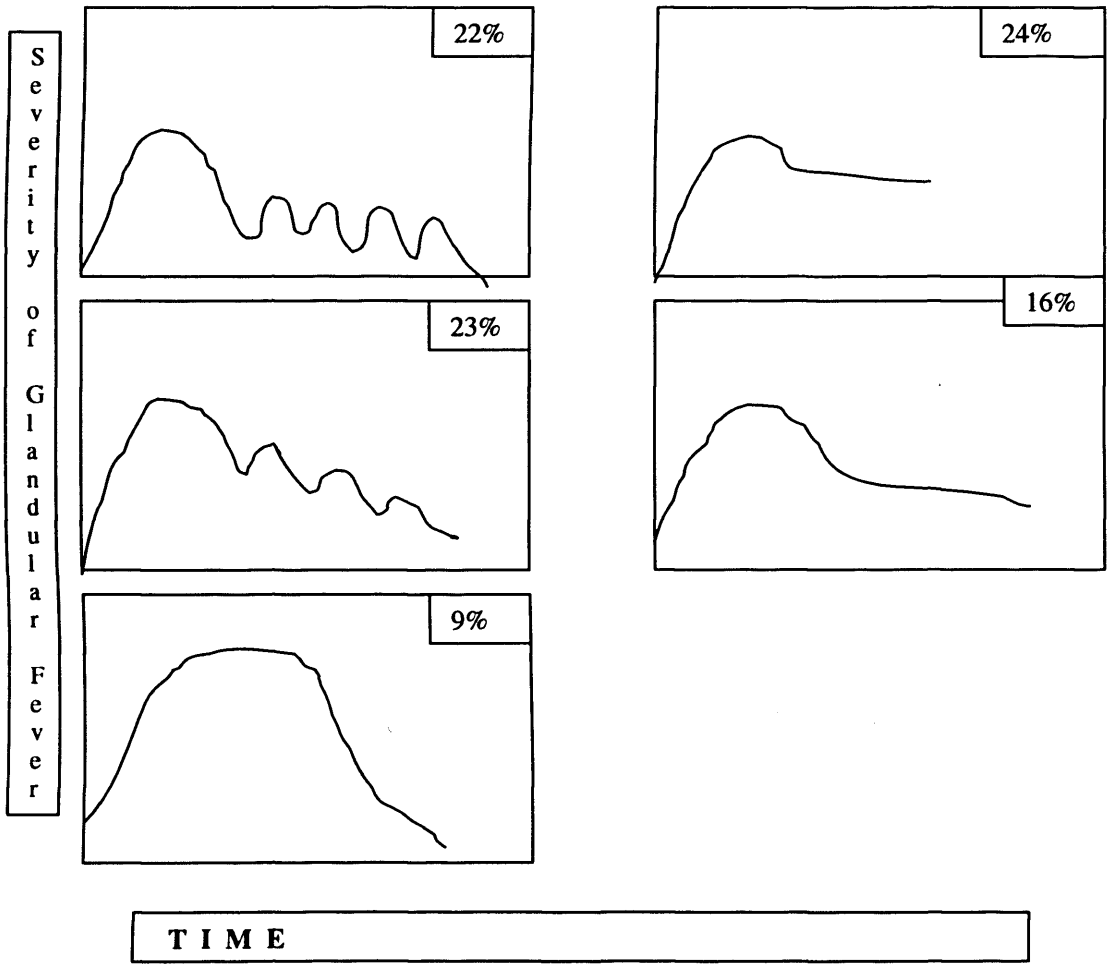
It can be seen from the above tables that participants diagnosed and still suffering from glandular fever indicate that the illness has had a significant impact on their behaviour. They believe that the illness has influenced the amount and quality of sleep, exercise and alcohol consumption and has rendered them more susceptible to other infectious illness. It could be, however, that the behaviour is influencing the recurrence of glandular fever, lack of sleep etc. lowering immune function and making them more vulnerable to recurrence of the illness. They report here that sleep and rest leads to improvements in health and that lack of sleep and stress leads to decrements in health. Most of the participants indicated that they experienced fairly frequent

recurrences of the illness with nearly three quarters of the sample (74%) indicating that they suffered recurrences at least once a month or more frequently. For the majority of the glandular fever participants, the past month has been either bad or average.

4.2.3 Progression of illness

Participants were asked to indicate which of the following trajectories best described the progression of their illness over time. % of the sample selecting each illness pattern is given in the top right hand corner of each box.

Diagrams to show perceived trajectory of illness.



4.2.4. Description of perceived illness trajectory

Less than 10% of the sample described their illness in terms of suffering the acute condition and then having a complete recovery from the illness. Nearly half (46%) felt that they suffered recurrences of the illness which was further divided into nearly half (23%) of these indicating that the recurrences became less severe as time went on and the other half (22%) describing the relapses as equally severe but with a return to normal health in between relapses. Nearly quarter of the sample (24%) described their illness as a severe acute illness with a small attenuation in the severity of the symptoms, but an ongoing, not relapsing condition (i.e. they experience the symptoms as continuous rather than fluctuating).

4.3 Summary and Discussion of Section 1

This section reported information on the subjective experience of glandular fever sufferers, their understanding of their illness and how it has progressed overtime. It has also provided information on sufferers' views on how the illness has impacted their lives and the behaviours that improve or exacerbate their health and the recurrence of this illness. Although there is information in the literature regarding the specific symptoms and psychological after effects of glandular fever, there is little information regarding the more specific effects of the illness on behaviour and lifestyle, and whether those suffering longer term effects of the illness experience those symptoms as constant or recurring.

The glandular fever participants in this study reported that their current illness states ranged from almost recovered to worse than ever. The level of severity of the illness was independent of the length of time since diagnosis but there appeared to be a consistent trend for the severity to increase as perceived stress, depression and emotional difficulties increased. This relationship could be in either direction with stress etc. influencing severity or severity influencing stress etc. More detailed differences between participants at

different stages of the illness on a range of psychosocial measures will be considered in more detail later in this analysis.

Although 42% of the glandular fever participants stated that they were almost recovered a further 42% stated that they were recovering with relapses; a large number (40%) reported that the severity of the illness in the previous month had been a bad. The symptoms reported during the first four weeks of illness were generally very high and conformed with an expected profile for people suffering from glandular fever. Over 90% of the sample had suffered from fatigue, sore throat and swollen glands and the vast majority suffered from physical weakness, headache and loss of concentration. Comparisons were made between the recovered group and the not recovered group in symptoms experienced during the first four weeks of diagnoses and there were not many distinguishing features. The only symptoms, experienced during the first four weeks of illness, which did distinguish the recovered group from the not recovered group, were the experiences of insomnia, anxiety, muscle ache and memory loss, with those who had not recovered from the illness suffering higher levels of these symptoms during the first four weeks of the illness. This could indicate that those who recover quickly are those who are somewhat less distressed and anxious and therefore able to sleep better and recover more quickly (A full list of symptoms, comparing the recovered group with the glandular fever group can be seen in Appendix A3.1).

The results of this study show that this illness had an important influence on quantity and quality of sleep and sufferers felt that it affected their ability to take exercise and drink alcohol. Lack of sleep, stress, other illnesses and having to concentrate were given as important factors in worsening of the illness. The relationship between negative aspects of the illness and psychosocial factors demonstrated that measures of psychological distress were associated with illness severity and frequency of recurrence in a systematic manner.

A novel finding in this study was the differences in the perceived trajectory of this illness. There were four main categories, two of which were

characterised by fairly frequent relapse in the severity of symptoms over time. In one group the relapses seemed to get slightly less severe each time and in the other group the relapses were described as being equally severe and that between relapses they were returning to almost normal levels of functioning. Only ten percent of the glandular fever group reported their illness in terms of having the acute illness and then having a return to normal functioning afterwards. The reason for this being a smaller number than has been found in other studies was to do with the way participants were recruited i.e. people who had been ill for some time were recruited as well as those recently diagnosed with the illness. A further group – again approximately one quarter of the sample – reported that their illness continued after the acute stage with the severity being slightly lower than at the acute stage but still at a fairly high level afterwards. The symptoms in this group were described as being continuous rather than fluctuating. Another group (16%) also described continuous, but less severe symptoms following the acute stage but with a clear gradual reduction in symptoms over time. It would appear then that the pathogenesis of this illness varies with 10% of this sample becoming ill and then recovering and approximately half of the remained suffering a fluctuating illness with recurrences and the other half suffering a more constant level of symptoms without the fluctuations. As participants also report an increased incidence of other infectious illness it might be that the recurrence of symptoms might be associated with the recurrence of other infectious illness.

Overall the participants in this study suffered from the classic symptoms of glandular fever on diagnosis with the illness having a significant effect on their lives and behaviour. Recovery for most was described as slow with the illness either continuing over an extended period or else suffering frequent recurrences over time. The next two sections focuses on differences between the glandular fever group as a whole and the (healthy) control group.

4.4 Section Two

Differences between the glandular fever and the control group on current health status and health behaviours

Groups were compared on issues of general health, health behaviours and current symptoms. The following table provides a summary of the differences between the groups, in particular between the glandular fever group and the healthy controls. The results for the glandular fever sufferers who reported that they had recovered from their illness were reported separately.

Table 11: Percentage of Glandular Fever sufferers and Healthy Controls reporting the following symptoms, illness, medication use and health behaviours

	Glandular Fevers N=55	Healthy Controls N=82
Allergies	27 (50%)	37 (46%)
A lot of colds in the past 12 months	19 (35%)*	9 (11%)*
A lot of sore throats in the past 12 months	31 (56%)*	7 (9%)*
Major past illness (now recovered)	9 (16%)	8 (20%)
Medication:		
Prescribed drugs	16 (21%)	14 (18%)
Over the counter drugs	22 (40%)*	14 (18%)*
Vitamins	24 (45%)*	18 (24%)*
Illness in previous month	29 (57%)*	2 (11%)*
Health Behaviours:		
Hours slept on average	8.2	7.7
Healthy Diet	2.54	2.46
Alcohol consumption:		
Regular drinkers	19 (34.5%)	34 (43%)
Moderate drinkers	31 (58.5%)	51 (65%)
Heavy drinkers	1 (2%)	3 (4%)
Smokers	7 (13%)	15 (19%)
Exercise:		
(How often do you Participate in the following		

sporting activities?)		
Aerobic	Mean Score = 0.8	1.2
	Never(0)=18(33%)	25 (28%)
	Sometimes(1)=21(38%)	30 (40%)
	Frequently(2)=16(29%)	27 (32%)
Mild exercise	Mean score = 0.6	0.3
	0= 35 (62%)	45 (74%)
	1= 10 (19%)	22 (21%)
	2= 10 (19%)	15 (5%)
Energetic exercise	Mean = 0.98	1.12
	0= 16 (29%)	27 (33%)
	1= 17 (31%)	31 (42%)
	2= 22 (39%)	24 (25%)

(These measures were taken after diagnosis with glandular fever)

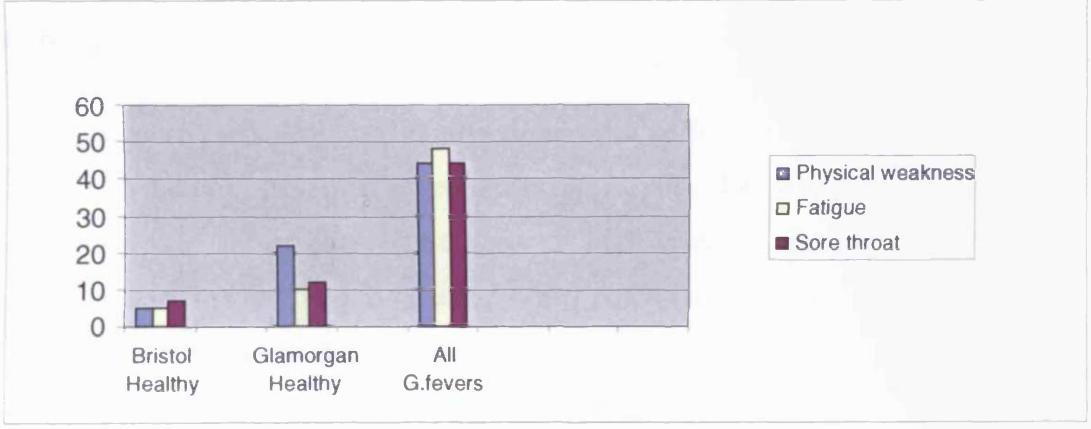
4.4.1 Summary of differences between the Glandular Fever Group and the Healthy Controls on health, medication and health behaviours

Overall, the glandular fever and control groups did not differ in terms of gender and age, major past illness. They were also matched for allergic status. Two of the healthy group stated that they currently suffer from a 'medical condition' as did one of the recovered group. These participants were removed from the subsequent analysis. Post hoc tukey tests revealed significant differences between the glandular fever group and the healthy group in reported frequency of colds and sore throats in the previous twelve months ($P<0.01$). There were little differences in the use of prescribed drugs but the glandular fever group took more over the counter drugs as well as vitamins than the control group (P0.01). The glandular fever participants slept slightly longer than the control group and the recovered participants. There were no major differences between the groups for reported health (risk) behaviours; healthiness of diets was reported as very similar. The glandular fever sufferers were only slightly more likely to report being light drinkers than the recovered participants or the control group, and the groups were very similar on numbers smoking. Levels of light exercise were similar across groups whereas energetic sport was highest in the recovered group and slightly higher in the control group than the glandular fever group but not significantly so.

4.4.2 Current Symptoms: controlling for the potential confounding effects of symptoms and confirmation of diagnosis

As well as identifying the characteristic symptoms experienced during the acute stage of the illness (see above), current symptoms were also measured. Symptom perception, although not necessarily an objective measure of health, may be seen as a measure of perceived health and well-being and was used to compare the glandular fever group with both the control group. This confirmed that about half of the Glandular Fever participants were currently suffering from the characteristic symptoms of this disorder. The control group were compared across locations in order to identify any effects of location on health status. The figure below considers three of the main symptoms of glandular fever (physical weakness, fatigue and sore throats) and makes comparisons within the control group across locations and between the glandular fever groups and the control group.

Figure 1: Differences in symptoms between Glandular Fever Participants and Controls and between Controls from Bristol and those from Glamorgan



(For a complete list of symptoms by health status and location see Appendix A3.1)

In comparing the glandular fever group with the healthy controls, it can be seen that they are clearly suffering more symptoms overall with nearly half of them still suffering from physical weakness, fatigue and sore throat. This suggests, however, that approximately half of the currently not recovered glandular fever participants were either in remission or not reporting the primary symptoms of the illness. From the data it can also be seen that the glandular fever participants were suffering significantly more 'other related symptoms' including headache and loss of concentration. (See Appendix A3.1). There appeared to be some location differences in the levels of symptoms with the healthy participants at Glamorgan reporting more symptoms than the Bristol healthy group. This finding is in line with socio-economic differences in health and indicates that participants from the more economically deprived area are reporting a greater number of symptoms. In order for these differences not to confound findings participants in the control group were classified into two categories – healthy controls and less healthy controls.

Two possible confounding factors were analysed to ensure that these variables did not influence the findings. These were allergies – of which there seemed to be quite high levels, and confirmation of diagnosis of glandular fever.

4.4.3 Allergies

Analyses were carried out comparing those who suffered from allergies with those who did not. Allergies are immune related disorders which could affect symptoms, etc. and because of the apparent high levels of allergy sufferers it was necessary to eliminate or control for any potential affect of allergic status. There were few significant differences overall between those suffering from allergies and those not suffering from allergies in either symptoms or psychosocial variables and it was considered appropriate to treat those participants suffering from allergies in the same way as other participants.

4.4.4 Confirmation of diagnosis

The majority (48 (81%) but not all of the cases of glandular fever, were confirmed by their General Practitioners (GPs). In order to assess the validity of the non-confirmed cases, analyses comparing confirmed cases with non confirmed cases were carried out. There were few significant differences between the two groups in the relevant variables and it was considered appropriate to treat those whose diagnoses had not been confirmed in the same way as those whose G.P.s had confirmed the diagnosis (for full details on the analyses of allergic status and confirmed cases see Appendix A3.2).

4.5 Summary and Discussion of Section 2

In this section it can be concluded that the groups did not differ significantly on health behaviours, apart from those directly influenced by the illness such as the amount of over the counter drugs and vitamins taken and frequency of other infectious illness. Health behaviours such as diet, exercise, alcohol, smoking and exercise, however, could not account for any differences which might be found between these groups. Furthermore, other important potential confounding variables were identified (such as allergies, living environment and confirmation of diagnoses) and these were further investigated and found not to be related to any differences between the groups. Having established that differences between the glandular fever participants and controls were not a consequence of health behaviours or other potential confounding variables, differences between the groups on current symptoms were investigated. As expected, glandular fever sufferers experienced high levels of the typical symptoms associated with their illness. The symptoms nominated by the glandular fever group were in accordance with symptoms established in previous studies to be associated with acute and chronic glandular fever. It was established that approximately half of the glandular fever participants, whilst reporting that they had not recovered from the illness, were currently not suffering from the primary symptoms of this disorder. This will be investigated further, later in the analysis.

Differences between the groups in symptoms not associated with glandular fever such as allergies were not significant.

The next section goes on to consider differences between the glandular fever participants and the control group on psychosocial variables.

4.6 Section Three

Differences between the glandular fever group overall and the control group on stress, psychological well being, personality, social support and coping strategies

ANOVAs were calculated to show differences between the control and glandular fever groups for a number of psychosocial measures. The following table shows that there were the anticipated differences between the groups on a range of psychosocial measures.

Table 12: Mean Scores (sd) for the glandular fever group and the healthy group on psychosocial variables

Variables	Healthy (N=31) Mean (sd)	Glandular fever (N=52) Mean (sd)
Stress Measures		
Major Life Events		
Negative *	1.8 (2.0)	2.7 (2.0)
Positive	1.3 (1.2)	1.5 (1.2)
Total Life Events *	3.1 (2.5)	4.2 (2.4)
Perceived Stress***	20.7 (4.6)	25.50 (7.1)
Hassles:		
Intensity ns	1.5 (0.4)	1.6 (0.4)
Frequency ***	12.4 (7.4)	22.2 (17.1)
Cumulative Severity ***	19.7 (16.2)	36.3 (27.0)

Mood & Disposition		
Depression (B.D.I.) ***	4.9 (5.1)	11.0 (8.6)
State anxiety***	30.5 (7.0)	40.1 (10.5)
Positive Mood ***	37.0 (10.1)	28.0 (10.0)
Negative Mood ***	15.0 (9.5)	23.2 (11.1)
Optimism *	32.1 (6.5)	28.7 (6.8)
Self esteem ns	58.5 (10.8)	54.6 (12.1)
Variables	**Healthy (N=31) Mean (sd)**	**Glandular fever (N=52) Mean (sd)**
P.F.R.S.		
Emotional difficulty ***	28.32(13.7)	48.16 (19.9)
Cognitive difficulty ***	18.13 (8.3)	31.08 (15.6)
Somatic symptoms ***	19.87 (5.4)	34.65 (14.2)

* = P<0.05 ** = P<0.01 *** = P<0.001

4.6.1 Summarising the differences between the Glandular Fever Group and the Healthy Control Group on the mean scores on the Psychosocial Measures

The table shows that there were very large significant differences between the control group and the glandular fever group on measures of objective (life events) and subjective (perceived) stress, personality characteristics, mood and fatigue related symptoms etc. The differences were very robust. Those suffering from glandular fever were significantly higher in negative life events in the previous 12 months than the control group and they were also scored significantly higher on perceived stress and the frequency and severity of minor daily hassles.

In terms of mood, the glandular fever sufferers were significantly more depressed than the healthy group. The groups differed significantly in mood state and dispositional optimism with the glandular fever group reporting higher negative mood and lower optimism. The groups did not differ

significantly in self esteem. The anticipated differences in the profile of fatigue related symptoms (PFRS) can be observed, with the glandular fever sufferers experiencing more fatigue, somatic symptoms, cognitive and emotional difficulties. There were no statistically significant differences between the groups on coping strategies and social support and therefore it was considered unnecessary to investigate the mediating role of these variables any further. (See Appendix A3.3)

Whilst these cross-sectional differences in psychosocial measures may not be particularly new or surprising, they confirm the high levels of psychosocial difficulties experienced by glandular fever sufferers and furthermore provide a baseline for the consideration of differences between different sub-categories of those with glandular fever. The next part of the analysis goes on to consider differences not just between glandular fever sufferers and healthy control group but between glandular fever sufferers at different stages of their illness.

4.7 Section Four

Differences between the Glandular Fever Participants at different stages of illness

A series of questions were posed in the section four introduction outlined earlier in this chapter. The questions refer to differences between the glandular fever participants at different stages of their illness. Those who were in the acute stages (i.e. recently diagnosed) were compared with those who had not recovered from the acute illness and who continued to suffer from the illness for a prolonged period. Before these questions could be answered the issue of defining and categorising the glandular fever groups was addressed .

4.7.1 Re-categorisation of the glandular fever group

There were essentially three possibilities for categorising the glandular fever group. The medical literature suggests that the acute period usually lasts for 6-8 weeks and conditions are considered chronic if the duration of symptoms, usually in attenuated form, persists for six months or longer (Carter & Penman, 1969). This would suggest a cut off point where the acute glandular fever participants were defined as those whose illness was less than two months duration and the chronics defined as those whose illness was greater than six months duration.

Previous research into glandular fever has used similar but slightly variable criteria for categorization. In looking at the distribution of the data a convenient cut point would be 0-3 months for an acute glandular fever group, 4-9 months for a 'middle group' and 10 months and more for a chronic group. Whilst symptoms subside after 6-8 week it is logical to assume that there is wide variation and that many patients who will not progress to the chronic stage will continue to be suffering acute symptoms for up to 3 months. Chi-square tests were carried out based on the two categorisations to measure symptoms and disease parameters across the length and time since diagnosis of glandular fever. The details of this analysis can be found in Appendix A3.4.

4.7.2 Question One – Symptom differences at different stages of the illness

The first question in Section four referred to whether symptoms were different in the chronic group compared with the acute stages of the illness. Whether the chronics continued to suffer the primary symptoms of sore throat, swollen glands, high temperature etc. and whether there were symptoms in the chronic condition that were different from the acute.

The pattern of symptoms was similar for both categorisations. Generally the symptoms attenuated as length of time since the illness increased, although this was not always the case. The overall pattern was the same regardless of how the categories were defined, the acute group had the highest level of symptoms followed by the middle group and then the chronic group.

The recovered glandular fever group were more in line with the control group and were therefore removed from the remainder of the analyses. The incidence of symptoms at different stages of the illness provided some interesting insights into the progression of symptoms over the time of the illness, however, the precise cut-off points did not appear to have a large effect on the results and it was decided to use the 'categorisation described below for further analysis as this provided a more even spread of numbers across the categories'.

4.7.3 Comparisons between glandular fever categories and the control group

The following categorisation was utilised in further analyses:
recovered (n=13)
acute 0-3 months (n=20)
middle 4-9 months (n=11)
chronic 10mths+ (n=19)

Using this categorisation of acute, 'middle-term' and chronic glandular fever. The differences between glandular fever symptoms at different stages of the illness and the healthy group were compared. There were significant differences between the healthy group and the glandular fever groups ge nerally, however, differences between the acute and chronic groups, whilst fairly consistent were not statistically significant. This may be due to the relatively small numbers in each of the categories.

Table 13: Current Symptoms In Healthy Controls And Glandular Fever Participants At Different Stages Of Their Illness

Current Symptoms	Healthy Controls	Acute G.fevers	Mid range G.Fevers	Chronic G.Fevers
Weakness ***	14%	**58%**	64%	**35%**
Excfatigue ***	8%	**58%**	46%	**41%**
Legs heavy***	12%	59%	42%	27%
Muscle Pain	17%	16%	36%	18%
Sore Throat ***	9%	**42%**	55%	**65%**
Headache ***	17%	**42%**	82%	**41%**
Sore eyes	21%	32%	27%	6%
Hot/Cold **	5%	**16%**	27%	**29%**
Sweating	5%	16%	18%	12%
Shivering	0	11%	0	0
Swollen Glands***	1	**37%**	36%	**41%**
Depression	8%	16%	18%	6%
Anxiety**	7%	26%	18%	0
Loss concentration ***	15%	52%	63%	65%
Loss memory	6%	11%	0	18%
Sleeping(hours) *	7.29	7.73	7.91	8.41

* = P<0.05 ** = P<0.01 *** = P<0.001

Where there are significant differences, these differences are between the healthy group and all three glandular fever groups. The differences between the three glandular fever groups did not reach significance.

There were no significant differences between the groups in:

Muscle pain

Joint pain

Nausea

Indigestion

Bloated stomach

Wind

Earache

Sore eyes

Noise and light sensitivity

Sweating

Memory loss

Allergies

(see Appendix A3.5 for full list).

4.7.4 Summary of differences in symptoms by Categorisation of Glandular Fever Participants

Results demonstrated significant differences in symptoms and functional status of the different groups mainly of course between the glandular fever and the healthy group where there were highly significant differences in the anticipated direction for relevant symptoms. The differences in total current symptoms across the three glandular fever groups were not high but the profile of symptoms varied somewhat The table above shows that most of the primary symptoms of glandular fever including sore throat, swollen glands, headache and loss of concentration was high in the acute group and even higher in the chronic group. Large numbers, although not all, of the chronic glandular fever group were suffering from the primary symptoms of the disorder. It is interesting to note, however, that large numbers of the chronic group are not suffering the primary symptoms although they have indicated that they have not recovered from the illness. Excessive fatigue and physical weakness are still high in the chronic group although they are somewhat lower than in the acute stage. The fact that the chronic group are highest in feeling hot and cold as well as suffering from sore throats could be indicative of higher levels of current colds and current upper respiratory tract infections in the middle and chronic groups. If you compare the acute glandular fever participants with the chronic glandular fever participants, there is an *overall*

attenuation of symptoms over time since diagnosis but the chronic group continues to have significantly higher levels of specific symptoms which are as high as – or even higher – than those in the acute condition. The findings are in line with previous research by White et al (1998) who reported persistent fatigue at 6 months in 10 % of patients who were diagnosed with glandular fever but not in those with upper respiratory tract infections. Excessive fatigue appears to be one of the major symptoms experienced by the chronic group with over 40% of them reporting it. Although this figure is higher than that found by White et al (1998), this is because the sample of chronic glandular fever sufferers in this study were those who had reported that they had not recovered fully from the illness. It would appear that approximately half of those who have been suffering from the illness for over six months and had not recovered fully were suffering a recurrence of the acute symptoms at the time of testing and it would be useful to consider the differences not only between the acute and chronic stages of the illness but also between those in remission from the primary symptoms of this illness and those who were suffering either a continuation over time of these symptoms or a recurrence of them at the time.

This analysis tells us that the groups did not differ on **non** relevant symptoms such as noise or light sensitivity, racing heart, earache, sore eyes, nausea, etc.. This is important because it demonstrates that the glandular fever group are not implying that they are higher in general symptoms. They are higher in symptoms related to the illness and these primary symptoms continue to be high in the chronic group. Other symptoms of the illness decrease somewhat over time but the chronic group are suffering from symptoms that could be associated with either glandular fever recurrence or the higher incidence of colds and upper respiratory tract infection.

4.8 Question 2. Differences in susceptibility to other infectious illness, perceived health status, and physical well being Susceptibility to other infections

It was noted that there were high levels of other infectious illness in the chronic glandular fever group and frequency of other infectious appeared to be an important issue in this illness.

Figure 2: Scores on 'a lot of infectious illness' for Glandular Fever Patients at different stages of their illness and the Healthy Control Group

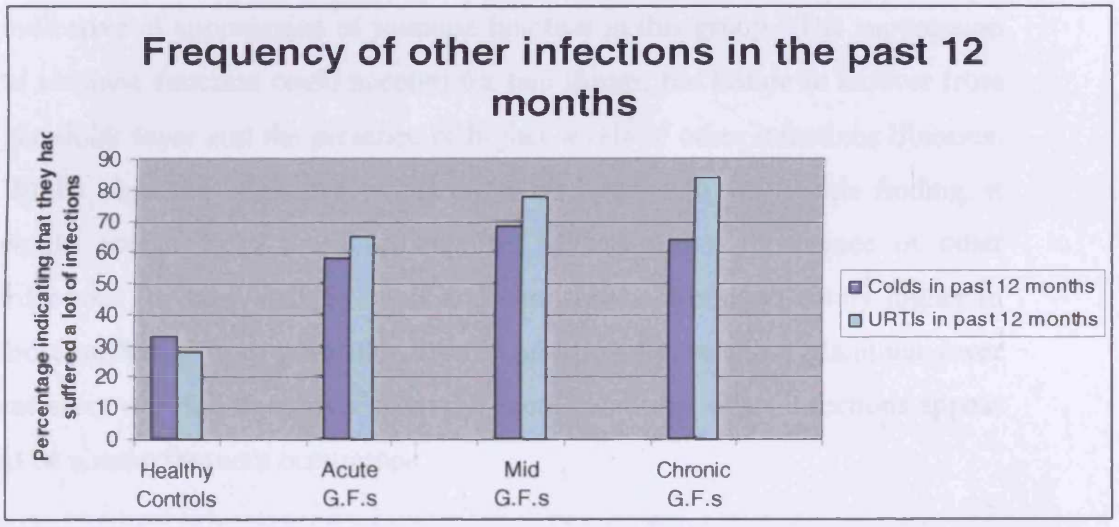


Table 14: Average number of infections in the past twelve months for Glandular Fever Participants at different stages of the illness and for the Healthy Control Group

(mean scores where 0=very few; 1=average no. of colds and 2=a lot of colds)

	Healthy Control	Acute g.fvrs.	Middle g.fvrs.	Chronic g.fvrs.	Significance
colds in past 12 months	0.7 (0.7)	1.2 (0.6)	1.4 (0.6)	1.3 (0.7)	P<0.0001
URTIs in past 12 months	0.6 (0.7)	1.3 (0.7)	1.6 (0.7)	1.7(0.7)	P>0.0000

For frequencies see Appendix A3.86

The significant differences were between the healthy controls and all three of the glandular fever groups. There were no significant differences between the different glandular fever groups.

In both cases, the glandular fever groups had been more susceptible to colds and sore throats in the previous twelve months than the control group. Susceptibility to sore throats appeared to be greater the longer the length of the glandular fever illness (i.e. the chronic glandular fever sufferers had a greater incidence than the acute sufferers although there was little difference between the middle and chronic group). If it is the case that those with glandular fever suffer a greater number of colds and sore throats this could be indicative of suppression of immune function in this group. The suppression of immune function could account for two things, the failure to recover from glandular fever and the presence of higher levels of other infectious illnesses. Whilst objective measures of infection are needed to verify this finding, it would appear from these self-reported illnesses that recurrence of other infectious illnesses such as colds and sore throats are significantly higher in those suffering from glandular fever. Additionally, in those glandular fever sufferers who fail to recover from the acute condition, other infections appear to be a more frequent occurrence.

4.9 Defining the glandular fever groups further – Case Definitions

The next part of the analysis considered the role of psychosocial variables and fatigue-related symptoms in further detail. On the basis of the previous analyses, further consideration was given to the case definitions of glandular fever and healthy participants (i.e. the control group). In particular, healthy controls were restricted to those who were not currently suffering symptoms of illness. There were differences in the glandular fever group which needed to be taken into consideration; it appeared that there were some participants who were currently suffering from the main symptoms of the acute illness (i.e. symptomatic) and other participants who, whilst had not recovered from the illness, did not appear to be suffering from the acute symptoms (i.e. asymptomatic). As discussed earlier in the thesis (Chapter 2) the Epstein Barr

Virus (as is characteristic of human Herpes Viruses) can lie dormant for long periods and be reactivated at different times. It was apparent that participants at different stages since diagnosis, whilst not fully recovered, may or may not be experiencing a relapse or reactivation of the illness. It was considered appropriate therefore to distinguish between those who were currently suffering acute symptoms of glandular fever, or reactivation of symptoms, separately from those who currently appeared to be in remission from such symptoms.

Consequently, the independent variables were identified as follows:

Glandular Fever, NO Symptoms (GFNOS) = those participants with infectious mononucleosis infection who were currently asymptomatic, i.e. they were not experiencing symptoms characteristic of the illness at the time of testing.

Glandular Fever, Acute Symptoms (GFACS) = participants who have been diagnosed with glandular fever in the previous 3 months who were suffering from typical symptoms of glandular fever at the time of testing, i.e. acute glandular fever sufferers.

Glandular Fever, Chronic Symptoms (GFCHS) = participants who had been diagnosed with glandular fever more than 9 months previously but who were suffering a recurrence of acute symptoms, i.e. chronic glandular fever sufferers.

Healthy control group (HEAL) = these were the control participants, who were healthy and who were currently not experiencing any symptoms of illness.

4.10 Analysis of Psychosocial Variables using newly defined Case Definitions of Glandular Fever

The psychosocial variables were re-analysed using the reorganised categorisation of illness status. There were a number of issues to consider in

this analysis but in particular the focus was on considering the following issues:

1. To improve our understanding of the prevalence of psychological distress in the acute and chronic stages of the illness.
2. To further our understanding of role of psychological stress, including stressful life events in the previous twelve months, current perceived social stress as well as daily hassles in acute and chronic glandular fever sufferers.
3. To investigate the role of coping strategies and social support.
4. To consider the differences in fatigue related symptoms in the acute and chronic stages of the illness.
5. Finally to consider whether there were differences between the currently symptomatic glandular fever participants and the non symptomatic sufferers on the above measures.

Is psychological distress associated with prolonged illness in general or is it more associated with recurrence of the main symptoms of the illness?

6. To investigate whether these differences are maintained when negative affectivity (NA) is controlled on the basis that evidence suggests that this relationship originates out of a tendency of those individuals high in NA to respond to self report methodologies with an overall negative perception (Watson, Pennebaker & Folger, 1987; Costa & McCrae, 1980).

ANOVAs and ANCOVAs were calculated to investigate the differences between these groups of participants.

Table 15: Mean Scores (SD) for Glandular Fever Groups and the Healthy control group on Psychosocial Measures (stress and hassles) co-varying negative affect (NA)

Variable	4. G.fvr Nosymps (N=32) Mean (sd)	3. G.fvr Acutes (N=6) Mean (sd)	2. G.fvr Chronics (N=10) Mean (sd)	1. Healthy Controls (N=30) Mean (sd)	*Post Hoc Tukey Test. Diffs between*
Perceived Stress ***	23.0 (7.4)	29.8(4.5)	28.3(4.2)	20.4(4.3)	*1 & 2* ** *1& 3* **
Covary NA***	25.1 (1.1)	29.6 (2.2)	29.3 (1.7)	19.3(1.0)	
Negative Life Events *	2.4 (2.1)	3.7(1.8)	2.8(1.9)	1.6(1.8)	*1 & 2* ** *1& 3* **
Covary NA ns	2.8 ((0.9)	3.6 (0.8)	3.0 (0.6)	1.4 (0.4)	
Positive Life Events ns	1.6 (1.1)	1.2 (1.6)	1.4(1.9)	1.3 (1.2)	
Covary NA ns	1.5(0.2)	1.2 (0.5)	1.3 (0.4)	1.4 (0.2)	
Total Life Events ns	4.0 (2.65)	4.8 (1.9)	4.2 (2.1)	2.9 (2.3)	
Covary NA ns	4.3 (0.5)	4.8 (1.0)	4.3 (0.8)	2.7 (0.5)	
Hassles:					
a. Intensity ns	1.5 (0.4)	1.9 (0.4)	1.6 (0.4)	1.5 (0.3)	*1 & 3* -
Covary NA *	1.6 (0.1)	1.9 (0.2)	1.6 (0.1)	1.4 (0.1)	
b. Frequency ***	17.0 (10.4)	27.2 (12.0)	33.1 (30.3)	11.8 (6.7)	*1 & 2* ** *4 & 2* *
Covary NA **	18.1 (2.8)	27.0 (5.8)	33.6 (4.5)	11.2(2.7)	
c. Cumulative Severity ***	*26.6(19.0)*	*51.0(21.8)*	*51.2 (40.8)*	*17.7 (25.8)*	*1 & 2* * *1 & 3* **
Covary NA *	30.7 (4.6)	50.5 (9.4)	53.2 (7.4)	15.5 (4.4)	*2 & 4* *

(For Post-Hoc Tukey test, significance at 1% level **; 5% level *; 10% level -)

4.11 Perceived Stress

The differences between the groups on perceived stress were highly significant (F value = 5.7; P<0.0003). It remained significant when negative affectivity was co-varied (F value 5.7; P<0.001). The post-hoc Tukey test revealed that the control group had significantly lower perceived stress than

both the acute and chronic glandular fever sufferers. The acute and chronic glandular fever sufferers both reported very high levels of perceived stress. The symptomatic chronic glandular fever sufferers reported higher levels of perceived stress than the asymptomatic chronic glandular fever sufferers, but this difference was not statistically significant. It is interesting to note that the non symptomatic glandular fever group were the only group not significantly different from the healthy group although they remain clearly and consistently higher.

4.12 Major Life Events

Differences in positive life events and total life events in the past 12 months were non-significant, whereas differences in negative life events were statistically significant (F value = 2.65, P<0.008). The trend was in the anticipated direction (acute, symptomatic, glandular fever sufferers reported highest level of negative life events and total life events, i.e. those currently suffering from glandular fever reporting the highest level of negative life events). The lowest number of negative life events, and total life events, were reported by the control group who were significantly lower than both the acute and chronic glandular fever groups. Again the non symptomatic glandular fever participants were next lowest in negative life events, after the healthy participants.

4.13 Minor Daily Hassles

The differences between the groups were highly significant for both frequency (F=4.82, P0.001) and cumulative severity (F=2.04, P<0.04) of daily hassles. The control group reported a significantly lower frequency and cumulative severity of daily hassles and also a lower intensity than both the acute and chronic symptomatic glandular fever sufferers. Intensity of hassles was highest for the acute glandular fever sufferers; frequency of hassles was highest for chronic glandular fever sufferers as was cumulative severity of hassles. It can be seen that daily hassles are significantly more problematic for those currently suffering from glandular fever than for the control group.

The asymptomatic glandular fever sufferers were less affected by hassles than the symptomatic glandular fever group. Those who had been suffering from the illness for some time or who had been suffering a reactivation (i.e. chronic glandular fever sufferers) suffered from a significantly greater frequency of hassles.

Overall, in terms of stress, the acute and chronic symptomatic glandular fever sufferers were similar. The chronic *symptomatic* glandular fever sufferers were more similar to the acute glandular fever sufferers than to the chronic *asymptomatic* glandular fever group, although all glandular fever groups reported higher levels than the control group. It appears that it is possible to distinguish between the chronic glandular fever sufferers who, by their symptoms, appear to be suffering a recurrence of the illness and those who (whilst not recovered) are not suffering from the acute symptoms. This group consistently reported lower levels of psychosocial stress and hassles than both the acute and chronic glandular fever sufferers on these measures of objective and subjective stress.

The next set of anovas and ancovas were used to analyse differences between the groups on measures of mood, depression and personality. The following table shows the levels of differences between the glandular fever categories and the healthy controls on measures of depression, mood, and aspects of personality.

Table 16: Mean Scores (sd) for Glandular Fever Groups and the Healthy control group on Psychosocial Measures (depression, negative mood, optimism and self esteem) co-varying negative affect (NA)

Variable	4. G.fvr Nosymps (N=32) Mean (sd)	3. G.fvr Acutes (N=6) Mean (sd)	2. G.fvr Chronics (N=10) Mean (sd)	1, Healthy Controls (N=30) Mean (sd)	*Post Hoc Tukey Test. Diffs between*
Depression (B.D.I.)***	8.8 (8.1)	18.3 (9.1)	10.7 (5.1)	4.3 (4.0)	*1 & 2 * 1 & 3 ** 1 & 4 * 2 & **3 2&4**
Co-vary NA ***	9.6 (1.0)	18.0 (2.1)	12.0 (1.7)	2.9 (1.0)	
Negative Mood**	20.7 (11.1)	30.7 (11.8)	23.7 (8.3)	14.1 (8.1)	*1 & 2 - 1& 3 ** 1 & 4 - 3 & 4 -*
Co-vary NA ***	25.1 (1.9)	30.2 (3.8)	25.8 (3.0)	11.9 (1.8)	
Positive Mood***	30.0 (9.6)	22.0 (6.6)	27.1 (11.0)	37.7 (9.6)	*1 & 2 * 1 & 3 ** 1 & 4 ****
Co-vary NA***	26.1 (1.7)	22.4 (3.6)	25.3 (2.8)	39.7 (1.7)	
Disposition Optimism**	29.5 (6.6)	25.5 (8.7)	29.2 (5.1)	32.8 (5.2)	*1 & 3 **
Co-vary NA***	27.3 (1.2)	25.7 (2.4)	28.0 (1.9)	33.9 (1.1)	
Self Esteem ns	54.2 (13.2)	54.8 (12.5)	57.4 (10.4)	59.5 (9.6)	*1& 4-*
Co-vary NA *	54.8 (2.3)	55.2 (4.6)	56.0 (3.6)	61.2 (2.2)	

* = P<0.05 ** = P<0.01 *** = P<0.001

(For Post-Hoc Tukey test, significance at 1% level **; 5% level *; 10% level -)

4.14 Depression

There was a highly significant difference between illness status and depression (F value=8.81, P<0.0001). This difference remained significant when negative affect was co-varied (F value 7.43, P<0.001). The differences between the control group and both the acute and the chronic glandular fever sufferers were highly significant; there were also significant differences between the acute and the chronic glandular fever sufferers as well as between the acute and non-symptomatic glandular fever sufferers.. Acute glandular fever sufferers were clearly the most depressed, followed by the chronic sufferers and then the asymptomatic glandular fever sufferers.

4.15 Mood states

The differences between the groups in mood states were highly significant in the familiar order (Negative mood - F value 4.45, P<0.002) (Positive mood – F value 5.57, P<0.0003). These significant differences remained when negative affect was co-varied (Negative mood - F value 5.13, P<0.000) (Positive mood – F value 5.06, P<0.000). It can be seen that the control group reported the most positive mood; the lowest positive mood was reported by the acute symptomatic glandular fever sufferers, followed by the chronic symptomatic glandular fever sufferers. The pattern of responses was in the anticipated order (i.e. control group; glandular fever sufferers not currently experiencing acute symptoms; chronic symptomatic glandular fever sufferers; and finally acute symptomatic glandular fever sufferers). The post-hoc Tukey test revealed a significant difference between the control group, and all other groups with the largest difference being between the control group and the acute glandular fever sufferers. For negative mood, as anticipated, the control group scored the lowest and the acute symptomatic glandular fever sufferers scored the highest; this was followed by the chronic symptomatic glandular fever sufferers and then the asymptomatic glandular fever sufferers. Table 15 shows differences between the groups on all three factors which were significant; the post-hoc Tukey test revealed significant differences between acute glandular fever sufferers and the control group; significant differences were also identified between chronic glandular fever sufferers and the control group, and between the acute glandular fever sufferers and the asymptomatic glandular fever sufferers.

4.16 Dispositional optimism and self-esteem

There was a significant difference in life orientation between the groups (F value 3.43, P<0.01). This difference remained significant when negative affect was controlled. (F value 9.29, P<0.001). The control group were significantly more likely than the acute glandular fever sufferers to have a generally optimistic outlook on life. Whilst there was no overall significant difference between illness status and self esteem, the control group had the

highest mean score for self-esteem. Again, for these variables it can be seen that the asymptomatic glandular fever sufferers can be distinguished from the chronic glandular fever sufferers. The pattern is consistent with this group being less depressed, experiencing less negative mood etc. than the chronic symptomatic glandular fever sufferers.

The next set of analyses of variance and co-variance considered differences between the groups on measures of emotional distress, somatic symptoms, cognitive difficulties and fatigue.

Table 17: Mean Scores (sd) for Glandular Fever Groups and the Healthy control group on Psychosocial Measures (profile of fatigue related symptoms) co-varying negative affect (NA)

Variable	4. G.fvr Nosymps (N=32) Mean (sd)	3. G.fvr Acutes (N=6) Mean (sd)	2. G.fvr Chronics (N=10) Mean (sd)	1. Healthy Controls (N=30) Mean (sd)	*Post Hoc Tukey Test. Diffs between*
Emotional Distress ***	40.0 (20.6)	52.5 (21.8)	41.8(12.0)	26.4 (8.9)	*1 & 3* ** *1 & 2**
Co-vary NA ***	47.8 (2.9)	51.6 (6.0)	46.3 (4.9)	22.3 (2.8)	
Cognitive Difficulty ***	27.5 (15.1)	45.7 (25.7)	31.3 (11.8)	17.0 (9.2)	*1 & 2* ** *1 & 3**
Co-vary NA **	30.4 (2.2)	45.4 (4.5)	32.7 (3.5)	15.5 (2.1)	
Somatic Symptoms ***	31.3 (13.2)	45.5 (17.6)	35.3 (12.4)	19.7 (5.4)	*1 & 2** *1 & 3**
Co-vary NA *	33.4 (2.2)	45.3 (4.4)	36.3 (3.4)	18.6 (2.0)	*3 & 4**
Fatigue ***	36.3 (17.8)	60.7 (16.7)	46.3 (12.4)	16.6 (6.5)	*1 & 2** *1 & 3**
Co-vary NA ***	39.4 (2.5)	60.6 (5.3)	36.9 (4.1)	15.8 (2.5)	*1 & 4** *3 & 4**

* = P<0.05 ** = P<0.01 *** = P<0.001 (For Post-Hoc Tukey test, significance at 1% level **; 5% level *; 10% level -)

4.17 Differences between the Glandular Fever Categories and Healthy Controls on the Profile of Fatigue Related Symptoms

The differences between the groups were significant for all the items in the Profile of Fatigue Related Symptoms. These remained significant when negative affect was co-varied (Emotional Distress – F. value = 7.84,P<0.000. Cognitive difficulty – F. value = 2.99, P<0.003. Somatic symptoms – F.value = 2.10, P<0.03. Fatigue – F.value = 1.19, P<0.000).

There were highly significant differences between the control group and the acute glandular fever sufferers on emotional distress, cognitive difficulty, somatic symptoms and fatigue; there were also significant differences between the control group and the chronic symptomatic glandular fever sufferers. The acute glandular fever sufferers reported the highest levels of emotional distress, cognitive difficulty somatic symptoms and fatigue (NB: in each case this was followed by the chronic glandular fever sufferers). The chronic symptomatic glandular fever sufferers were followed more closely by the asymptomatic glandular fevers and then the control group. A post-hoc Tukey test revealed significant differences consistently between the control group and the acute glandular fever sufferers; significant differences were also identified between the acute glandular fever sufferers and the asymptomatic glandular fever sufferers. Again, the pattern identified above, of a reduction in problems in the asymptomatic glandular fever sufferers, was again observed.

The next set of analyses considered differences between the case definitions of glandular fever sufferers and the control group on the possible mediating variables of coping and social support

4.18 Social Support and Coping Strategies

See Table A3.7 in Appendix for details of this analysis.

There were no overall significant differences between health status and social support. The issue of social support as mediator or as a cause of psychological stress has been discussed earlier. Because of the lack of any significant findings for this variable, it was not considered necessary to

investigate further the precise role of social support in this stress illness relationship. There were also very few differences in the use of coping strategies, however, some differences were found in the use of confrontive coping and social support as a coping strategy. Social support was the most commonly used coping strategy and there was a significant difference between the symptomatic and asymptomtic glandular fever sufferers using this coping strategy. The acute glandular fever sufferers used more confrontative coping than both the chronic glandular fever sufferers and the asymptomatic glandular fever sufferers. Interesting trends can be seen in the differential use of coping, for example acute glandular fever sufferers seem more likely to use escape avoidance strategies and the control group are most likely to use problem-focused strategies. This is in line with the literature on problem focus and emotion focus coping strategies (Lazarus 1966).

4.19 Summary and discussion

A clear pattern emerges from the cross-sectional analysis of the psychosocial data. Those participants currently suffering from the acute symptoms of glandular fever and those suffering from either a recurrence of the acute symptoms or a failure to recover from glandular fever are suffering from significantly higher levels of psychosocial stress and emotional distress than the (healthy) control group; The non symptomatic glandular fever group were consistently lower in the psychosocial measures than the symptomatic glandular fever groups, although generally not quite as low as the healthy group.

Many of these findings support the work of White et al (2001) who found evidence for a fatigue syndrome following glandular fever (between 9 & 42% were said to develop fatigue and chronic fatigue syndrome following a triggering infection which included glandular fever). The fatigue syndrome reported by White consisted of symptoms of physical and mental fatigue, retardation, hypersomnia, poor concentration, psychomotor retardation, irritability, social withdrawal, emotional lability as well as transient sore throat and swollen glands.

An aim of this study was to investigate the after-effects and pathogenesis of glandular fever and to consider the clinical picture at different stages of the illness. It can be seen that there is substantial evidence that high levels of physical symptoms of fatigue, cognitive difficulties, and psychological distress in patients diagnosed with glandular fever, and in a substantial number of these people with glandular fever, these psychological difficulties continue for a long period of time after the acute stages of the illness. Those reporting a failure to recover from the early diagnoses of glandular fever suffer continued physical symptoms of fatigue and cognitive difficulty as well as psychological distress. Whilst this is not a new finding, it supports earlier research by White and others mentioned earlier, however, what is new is that in those who report a failure to recover there appear to be important differences in psychosocial factors, depending upon whether or not they are currently experiencing the primary symptoms of the disorder. This group demonstrate a pattern of psychosocial and physical well being more similar to those in the acute stages of the illness.

Associated with this was the self described trajectory of the illness. Again, participants suffering from glandular fever perceive the progression of glandular fever either as one of frequent recurrences of the disorder and or as a continuation of the illness without the fluctuations.

The overall finding was that levels of distress were somewhat attenuated, but usually not significantly less, in the chronic condition than in the acute phase of the illness which might indicate a role for psychological distress in the recurrence of symptoms. It is certainly clear from this cross-sectional analysis that there is an association between acute glandular fever and psychological distress as well as a continued role for psychological distress in those failing to report a full recovery from the initial illness (as well as in those suffering a recurrence of the disease). Psychological distress was lower in those who were suffering from chronic glandular fever, but who currently were not experiencing the primary symptoms of the disorder, than in those who were. The glandular fever group who were currently not suffering from the primary

symptoms tend to be somewhat lower in psychological distress than the chronic glandular fevers who were currently suffering symptoms, but nevertheless consistently higher than the control group. It appears that those suffering the chronic condition fluctuate in their symptoms but appear to have high levels of psychological distress and/or discomfort including more, depression, negative mood, negative life events, cognitive difficulties, emotional distress and somatic symptoms. The question of whether these psychosocial differences are associated with vulnerability to this illness or a consequence of it cannot be ascertained from this cross-sectional analysis. All that can be concluded is that there were significant differences between the control and illness groups and that whilst there is an attenuation of psychosocial difficulties in chronic glandular fever and even more so in the currently asymptomatic groups, these sufferers continue to experience higher levels of distress than the control group. Wessely et al (1998) demonstrated that those who rated themselves as significantly fatigued and or psychologically distressed prior to a diagnosis were substantially more likely to go on to develop either chronic fatigue or chronic fatigue syndrome. What needs to be taken into consideration in this analysis, was psychosocial status prior to diagnosis. There was a trend for those suffering from glandular fever to have suffered more negative life events in the previous 12 months but this difference did not reach significance. Furthermore, the problem of retrospective reporting of negative events in people who are suffering from an illness needs to be taken into consideration in this type of analysis. There did not appear to be major differences in the personality characteristics of the participants as measured by self esteem and dispositional optimism.

White reported that depression at six months was distinct from fatigue at six months with depression being associated with pre-morbid psychiatric disorder, social adversity and emotional personality. In this study there appeared to be an association between both acute and chronic illness and levels of depression. Whilst the issue of association with premorbid psychiatric illness was not investigated levels of depression in the chronic sample in this study were significantly higher than in the control group. This suggests that unless the sample comprised a significantly higher level of

participants with a prior psychiatric history, then depression is associated with the chronic stages of the illness as well as with the acute stages.

The issue of recurring viral illness in the chronic glandular fever sufferers is an important feature of this disorder identified in this study. This provides support for the view that immunosuppression is a factor in the progression of this illness with those not recovering from the both the acute condition and those with chronic glandular fever suffering frequent recurrences of other infectious illness.

Whilst it is possible that this could be a consequence of higher symptom reporting in the glandular fever group, the symptoms reported were specific to infectious illness and they did not report high levels of other random symptoms. It was, in fact, the chronic glandular fever group who experienced the highest levels of recurrence of other infectious illness. What needs further clarification is whether the recurrences of symptoms of glandular fever are distinct from recurrence of other infectious illness or whether there is some connection between the two.

This study provides support for previous research findings of a high incidence of fatigue and psychosocial difficulties in a significant proportion of sufferers of glandular fever. There were important differences between those acutely ill and the controls, as might be expected, but there were also substantial numbers who failed to recover and whose physical and psychological difficulties continued to be significantly worse than the healthy controls and whilst attenuated were not significantly worse than those in the acute stages of their illness.

The findings from this study suggest that the methodology and measures used here are appropriate for studying the role of psychological factors in the progression of viral illness. Interesting findings emerged from the cross-sectional analysis and comparisons between people at different stages of the illness (whilst controlling for potentially confounders) yields important information regarding differences between those suffering from glandular

fever and the control group as well as between glandular fever sufferers at different stages of the illness. What is needed, however, is a measure of the changes over time in psychosocial measures and illness measures in order to understand any causal relationship between psychosocial factors and illness recurrence. This longitudinal analysis of glandular fever participants was attempted but, as is explained more fully in the next section, this proved to be problematic. The next section describes the longitudinal study and the problems experienced conducting this study.

4.20 Longitudinal Study of Glandular Fever Sufferers

The aims of this study were to follow up those suffering with glandular fever identified at time one (i.e. when first surveyed) in order to investigate the progression of the disorder and changes over time.

4.20.1 Procedure

Participants were contacted 3-5 months after the initial interview and asked to participate in a follow-up study. An appointment was made for participants to return to the testing centre to complete a second battery of tests and complete another set of questionnaires.

The follow-up questionnaire (i.e. for time two) asked for information concerning the following: (a) changes in health and behaviour since the last interview, (b) how the illness had progressed, together with (c) current symptoms and (d) a series of standardised paper-and-pencil tests which required participants to report certain events, feelings and behaviour over the previous month and/or week.
The procedures were generally the same as for the first study.

4.20.2 Design

This study was a prospective, longitudinal study which followed students over time in order to track the progression of their illness and to evaluate whether variables at time two had improved or become worse than at time one. Also

to investigate the relationship between psychosocial variables at time one and illness status and symptom perception at time two.

4.20.3 Participants

The number of participants at time two was: 17 glandular fever sufferers, and 16 healthy control participants. Of those who returned for time two, five were excluded from the study due to incomplete data. The total number of participants at time two was 28 participants. This compared with the total number of participants at time one which was 142. This included 32 glandular fever patients without primary symptoms, 6 glandular fever sufferers in the acute stages of the illness, 10 glandular fever patients in the chronic stages of the illness, 64 healthy controls with symptoms and 30 healthy controls without symptoms. It can be seen that there was a substantial drop out of participants between time one and time two.

4.21 Limitations

Students are a transient population and conducting a longitudinal study using students is inherently problematic. There was a high drop out rate at this stage largely due to difficulties locating students. Many had changed accommodation and not left forwarding addresses, some had moved away from the area completely; 2 had been involved in a car accident, a further 2 had developed other illnesses and were unable to continue with the study, and 2 more had suspended studies due to having missed so much time because of their health.

Another difficulty was controlling the time scale for follow up. Students were often unavailable at critical times for testing (i.e. during examination periods or during holiday periods, Easter, Christmas and the long summer vacation). These factors had a significant influence on numbers in this of the study. The majority of these types of studies are conducted at clinics which participants attend for diagnosis and treatment and although there are clear advantages to a community study of this disorder, (avoiding the bias of self referral for

treatment) the disadvantages of high drop out rate caused significant problems for following these cases.

The table below first of all shows the two sets of scores for psychosocial measures taken at time one. These are the scores for the whole group compared with scores (at time one) for the sub group who had returned for the follow up study.

Secondly, this table shows the scores on the psychosocial measures at time two for the returning participants. This allows consideration of differences in the initial scores between the returning group and the whole group as well as differences between the sub group time one scores and their time two scores.

Table 18: Mean Scores on Psychosocial Measures at Time One for the whole sample and at Time One for the sub sample of returning participants as well as Time Two scores for this sub-group

Variable	G.fvr Nosymps (N=4)	G.fvr Chronics (N=9)	Healthy Controls (N=7)
Perceived Stress:			
Time One (whole group)	23.0	29.8	20.4
Time One (sample)	17.75	21.00	24.22
Time Two	18.25	20.14	24.11
Hassles:Intensity			
Time One (whole group)	1.51	1.90	1.46
Time One (Sample)	1.31	1.52	1.43
Time Two	1.44	1.51	1.21
c. Frequency			
Time One (whole group)	16.97	27.33	11.0
Time One (Sample)	4.75	31.11	10.86
Time Two	7.0	18.67	14.0
a. Cumulative Severity			
Time One (whole group	26.56	51.51	17.67
Time One (sample)	6.50	45.78	16.13
Time Two	10.0	28.56	17.0
Depression			
Time One (whole group)	8.84	18.33	4.33
Time One (sample)	5.0	8.67	5.86
Time Two	3.75	7.22	6.0

Negative Mood			
Time One (whole group)	20.67	30.67	14.07
Time One (sample)	13.50	22.67	14.71
Time Two	9.0	17.78	12.85
Emotional Difficulty			
Time One (whole Group)	40.00	52.50	26.43
Time One (sample)	27.25	43.78	26.86
Time Two	24.75	41.67	29.43
Cognitive Difficulty			
Time One (whole Group)	27.45	45.67	17.0
Time One (sample)	22.00	30.44	18.29
Time Two	24.50	26.22	19.29
Fatigue			
Time One (whole Group)	36.37	60.67	16,57
Time One (sample)	42.50	46.33	17.57
Time Two	25.0	32.56	24.14
Somatic Symptoms			
Time One (whole Group)	31.35	45.50	19.67
Time One (sample)	26.25	34.22	18.43
Time Two	20.75	23.89	24.86

4.22 Discussion of Longitudinal Study and Implications for further studies

Before considering changes between time one and time two, scores for the sub-sample of returners were compared with the whole group at time one. When comparing the time one scores for both the glandular fever groups, the time one scores for the subset of returners were significantly lower than the whole group at time one. It was clear that those who had returned for the time two session were the ones who were nearly recovered, who were scoring much lower at time one on the psychosocial variables and who were the least psychologically distressed at time one (i.e. it was not a representative sub-sample who were able to return for the time two session later). This group were less severely ill and suffered fewer symptoms at time one. There were no significant changes between time one and time two in this 'atypical' sub group in perceived stress, depression and emotional difficulties; given that they were substantially lower on these measures than the total sample at time one. This group showed reduced cumulative severity of daily hassles, negative mood and somatic symptoms, indicating that the group were less ill

and less psychologically distressed, and there were some further improvements in stress and well-being over the three months.

In considering the challenges posed by this investigation it was clear that further investigation of the role of psychosocial stress in the progression and recurrence of viral illness was an interesting and important area for further research. In considering the difficulties of conducting longitudinal research with glandular fever patients (due to the long time scales involved) consideration was given to studying a similar but more frequently recurring virus with similar characteristics to the Epstein Barr Virus (EBV).

It was decided that Herpes Simplex Type 1 (HSV) would be a relevant virus to consider longitudinally due to (a) it being a member of the same family of viruses as Epstein Barr Virus (herpes virus), (b) the frequent nature of recurrences of this virus, (c) the fact that it is a relatively common virus and (d) the lack of longitudinal research considering the role of psychosocial factors in recurrence of the virus.

It would be possible to study this virus longitudinally using diary methodology which overcomes some of the difficulties associated with frequent visits to the side of testing. Diary study methodology is an efficient way of collecting longitudinal data of this type.

Other interesting consequences of this pilot study were as follows:

1. The frequency of recurring colds and infectious illness in chronic glandular fever participants and the implications of this? Does it suggest that in the chronic condition glandular patients have recurring symptoms and recurring infections due to suppression of immune function? Is this associated with high levels of stress? Are the recurrences of symptoms of glandular fever being mistaken for recurrence of other infectious illnesses.
2. The relationship between chronic glandular fever and chronic fatigue syndrome could be addressed because the symptoms in the chronic glandular fever patients were very similar to those in chronic fatigue

syndrome; Another issue concerns the ongoing issue of EBV-onset Chronic Fatigue Syndrome. It would be interesting therefore to consider the role of psychosocial factors in the pathogenesis of CFS and the issue of EBV-onset and other-onset CFS as well as the issue of recurring infectious illness in chronic fatigue syndrome.

Another aim of this study was to investigate the similarity between chronic glandular fever and chronic fatigue syndrome. A further study was needed to investigate differences between CFS patients with differing onset, in particular differences between those whose CFS was precipitated by EBV and those whose illness was precipitated by other virus and/or other factors. Another issue was the role of recurring infectious illness in chronic illness, and this would also be considered further in both HSV infection and CFS.

4.23 Conclusion

The findings of this study support previous research on the relationship between acute and chronic glandular fever and psychological and physical deficits. The findings extended this research to provide more detailed explanations of the effects of the illness on lifestyle and behaviour as well as the perceptions of sufferers regarding the progression of their illness. A novel aspect of this study was the distinctions drawn between the symptomatic and non symptomatic glandular fever sufferers and suggestions that future research take this difference into consideration when investigating the after effects of this illness. In particular the potential confounding of the recurrence of glandular fever and the recurrences of other infectious illness needs verification using more sophisticated techniques to identify specific viral recurrence. The methodology used in this study proved to be an effective way of investigating this problem and formed the basis of the methodology used in further studies in this thesis. The next study of Herpes Simplex was informed by the methodology used in this study. In particular the initial cross sectional study of HSV utilizes the same measure as this study. The study will be extended to investigate the longitudinal relationship between psychosocial factors and illness recurrence.

CHAPTER 5

5.1 The role of psychosocial factors in the recurrence of herpes simplex virus

5.2 Progression from Study One

The first study in this thesis considered the role of psychosocial factors in the progression and/or recurrence of Epstein Barr virus. The findings supported the view that those who were suffering from glandular fever were significantly higher than a healthy control group on stress and a range of measures of psychological distress. The optimal way of studying the causal relationship between stress and illness is to investigate changes over time in psychosocial factors and how these relate in time to recurrence of disease. In the initial study of glandular fever, cross-sectional differences were considered between a healthy control group and the glandular fever group, and between the glandular fever participants at different stages of the illness. Due to a number of practical problems, the attempt to investigate changes in psychosocial factors and glandular fever recurrence longitudinally proved problematic. The study did support the view that there was a significant relationship between chronic glandular fever and high levels of stress and emotional distress, however the cross-sectional design did not allow for any causal relationships to be demonstrated. The study reported in this section of the thesis attempts to overcome some of these difficulties by considering the recurrence of another herpes virus, herpes simplex type 1. This virus is possibly less severe in its recurrence, but can recur frequently and its recurrence can be quite easily verified.

The first study of herpes simplex is a cross sectional analysis of differences between the herpes group and a healthy control group. This study largely replicates the methodology used in the study of glandular fever.

5.3 Introduction

The overall aim of this thesis was to investigate the relationship between psychosocial factors and the recurrence of viral illness. The evidence, from both human and animal studies, supports the view that the immune system is functionally integrated with both the central nervous system (CNS) and the endocrine system (e.g. Ader, Felten & Cohen, 1991) and a number of studies have now demonstrated the impact of psychosocial stress in the modulation of both humoral and cellular immunity via neuroendocrine immune interaction (e.g. Cohen & Williamson, 1991; Kiecolt Glaser & Glaser 1991, Segerstrom & Miller 2004).

Evidence regarding the role of psychosocial stress as a risk factor in the development and duration of primary herpes virus infections suggests that individuals who are more distressed have more frequent recurrences of Herpes Simplex Virus types 1 (HSV-1) and 2 (HSV-2). (Luborsky et al 1976, Goldmeir and Johnson 1982). This chapter aims to provide a brief overview of the pathogenesis of HSV infection and the immune response it generates as well as highlighting the evidence that investigates the relationship of psychosocial factors to the recurrence of HSV recurrence and some of the methodological problems with this research.

5.4 Herpes Simplex Virus Infection - An Overview

HSV is said to be a natural pathogen of humans characterized by its ability to cause an acute infection at a peripheral site and establish a latent infection in the local sensory ganglia which innervate the site of the initial infection (Blyth & Hill 1985). The hallmark of infection with HSV is its ability to spontaneously reactivate from this quiescent, non-infectious latent state and cause a recurrent infection in the periphery at, or near, the original site of infection. (Hill 1985). Most recurrent infections are due to reactivation of this endogenous, latent virus rather than exogenous re-infection (Whitley 1990). Importantly then, the latent state can be interrupted by a triggering factor and is capable of periodic reactivation in 90% of those infected.

Although HSV reactivation and recurrent infection typically occur spontaneously, correlations have been made between reactivation and physical or emotional stress, fever, exposure to ultraviolet light, tissue damage and immune suppression (Hill, 1985). The frequency with which reactivation occurs varies enormously among individuals although each reactivation does not necessarily result in the development of clinical symptoms.

Recurrences are said to vary enormously in frequency from 4 to 35 a year with a mean duration of eight days (Luby & Klinge 1981). Unlike other common viruses, the individual will remain latently infected for life following primary infection with HSV.

The virus is transmitted by contact of mucous membranes, lesions or during viral shedding in asymptomatic people (Harger, Pazin & Breinig 1986). There is no cure currently available only palliative treatment, the most common being the antiviral drug Acyclovir.

HSV types 1 and 2 are among the most prevalent infectious agents in humans, producing a wide variety of clinical manifestations (Klein 1976). It has been estimated that up to a third of the world's population has recurrent episodes due to HSV and that over one half of these patients have more than one attack each year. (Klein, 1976). Although not a life threatening condition, the recurrence of herpes, whether it be facial or genital, is an important medical problem which has significant implications for many people. Whilst there is much anecdotal evidence regarding the role of psychosocial factors in herpes recurrence, empirical evidence regarding the role of psychosocial factors is patchy. The precise role of psychosocial factors in relation to the recurrence of the virus remains poorly understood and there is even less information regarding the psychological and cognitive effects of this virus.

The immune defence mechanisms of the individual may influence both the acquisition and the severity of primary HSV infection as well as the development, maintenance and reactivation of latent HSV. Naturally occurring and experimentally induced defects in cellular immunity have been

shown to result in enhanced risk of primary and reactivated HSV infections (reviewed in Rinaldo & Torpey 1993). If cellular immunity is important for control of HSV infection and latency then it logically follows that stress-related decrements in cellular immunity may impact on the control of latent HSV infection. The evidence however is more anecdotal than empirical and there appears to be significant heterogeneity in the research findings to date.

5.5 A Review of the Evidence for the Role of Psychosocial Factors Affecting Herpes Simplex Virus Infections

A number of studies have investigated the relationship between a range of psychosocial factors and their relationship to HSV. Depressed psychiatric patients have been found to have significantly higher herpes virus antibody titers than nonpsychiatric controls (Schliefer et al., 1985) whereas no differences between patient and control groups were found when antibody titers to other viruses were assayed, for example measles or rubella (Lycke, Norrby & Roos, 1974). This could be associated with the fact that herpes virus can recur when the immune system is suppressed whereas activation of measles or rubella is associated with exposure to the relevant virus.

In a meta-analytic review of the relation of stressors and depressive symptoms to the progression of two immunologically moderated diseases (i.e. the recurrence of HSV and the progression of Human Immuno Virus (HIV)), Zorilla and colleagues (Zorilla, McKay, Luborsky & Schmidt, 1996) concluded that depressive symptoms, but not stressors, may have some value for predicting subsequent episodes of HSV recurrence. In this review they attempted to (a) 'quantitatively determine' whether the evidence reviewed in the studies supported a critical role for stressors and/or depressive symptoms in HSV, (b) establish the 'robustness' of that relationship and (c) identify potential moderating factors which may explain some of the discrepant findings existing in this literature.

5.6 Genital Herpes vs Oral Herpes

The review was based upon fifteen studies of HSV, only 3 of which were investigations of oral herpes; the remainder were studies of genital herpes. They found that most studies of HSV tend to have cross-sectional designs and typically involve Caucasian women in their twenties who have had some college education. The main focus of the studies reviewed, and this is typical of research on HSV, was primarily on recurrent *genital* herpes and most relied exclusively on the patient's self report as the indicator of HSV recurrence. Many studies did not report on the use of concurrent antiviral medication and those that did excluded medicated patients.

In relation to the differences between the 'stressor studies' that they examined, and those studies focusing only on depressive symptoms and HSV recurrence, the former contained proportionally more men and somewhat older subjects. Furthermore, stressor studies were *less* likely to have a prospective design (only 3 of them did) and more often examined the recurrence of genital herpes as opposed to oral herpes.

Across all studies reviewed, both depressive symptoms and stressors were modestly related to HSV recurrence however prospective studies observed significantly smaller correlations than the cross-sectional design studies. There was however some diversity in the findings with prospective studies providing less support for the relationship between increased HSV recurrences in stressed subjects. In contrast, prospective studies indicated a greater recurrence of HSV associated with depressive symptoms. As mentioned above there were only 3 prospective studies of stressor and HSV recurrence in total in this review, an issue to be returned to later. The analysis indicated that the evidence was not sufficiently robust to predict confidently that future studies would generate similar findings, and more research utilising prospective designs is required as a matter of some importance in this area.

5.7 Frequency and Severity of HSV Recurrence

Subject characteristics appeared to moderate the relation of psychosocial factors to HSV recurrence and may therefore provide some explanations for the heterogeneity observed in the stressor studies. Those that reported excluding medicated patients and those that used predominantly female participants observed a smaller relation between psychological factors and HSV recurrence. Furthermore, studies that used older groups (i.e. over 30) also observed a smaller relation between stressors and HSV recurrence than those examining younger groups. It may be that in the older groups there is a natural decline in the frequency and severity of recurrence of cold sores or that they have adapted mechanisms to deal more effectively with it. It could be that severity or frequency of recurrence is an important factor in the relationship between psychosocial factors and recurrence, however this factor has not been taken into consideration in any of the studies reviewed here. There are clearly large variations in how much people suffer from cold sores both in terms of the number of episodes they suffer and in the severity of each outbreak.

Studies that examined the relation of depressive symptoms to the recurrence of oral or facial herpes obtained smaller effect sizes than those studies that investigated genital herpes however this may reflect the fact that oral herpes studies were far fewer and more likely to verify recurrence.

5.8 The Nature and Measurement of Personality Traits and other Psychosocial Variables

Few studies have focused on psychosocial factors other than depressive symptoms and stressors, and these stressors may not always be major determinants of emotional distress and, consequently, immunologic change. The stressors and depressive symptoms may be transient in existence and therefore in their effects. Furthermore, as discussed in the previous chapter there is a need to measure not only the frequency of actual stressors but also the cognitive appraisal of those stressors. The review suggests that further

research should study stable, *enduring* psychosocial factors that render individuals vulnerable to more sustained or at least repeated immunosuppression. Furthermore, the emphasis in these studies on 'stressors' without taking into consideration other important variables such as subjective perceptions of those stressors, coping strategies and social support is a significant omission in this literature. One reason why the studies of depressive symptoms were more robust may be due to the possibility that depressive symptoms were in fact a better measure of emotional distress (possibly as a consequence of a failure of adaptation to stress) than a measure of actual stressors, which fails to take into consideration individual differences in appraisal of, and adaptation to, these stressors.

Future research in this area should focus on sufferers who are higher on 'enduring psychosocial vulnerability factors' (EPVF) who, it might be predicted, would suffer greater recurrence of HSV-1 infections than those subjects low on these factors. These EPVFs would include measures of stable psychosocial traits (e.g. depression, self esteem, trait anxiety), as well as cognitive appraisal of stressors (perceived stress).

There is further evidence that these enduring psychosocial traits may act as a vulnerability factor in the relationship between stress and infectious illness via an increased susceptibility to the immunosuppressive effects of stressors. Persistent vulnerability factors appear to moderate the effects of stressors on HIV progression (e.g. chronically depressed HIV positive men have been found to experience greater rate of CD4* cell decline than non chronically depressed (Zorilla et al 1996). Similarly, the relationship between stress and immune function resulting in recurring infectious illness might by greater in people with Chronic Fatigue Syndrome (characterised by enduring psychosocial traits such as depression and anxiety).

5.9 The Focus on Genital Herpes and Further Implications (i.e. sampling bias and differential effects)

A more recent review by Shah and Button (1998) again focused on studies investigating the relationship between psychological factors and reactivation

of HSV although they use only studies investigating *genital* herpes virus. In terms of their clinical features HSV1 and HSV2 are indistinguishable although there is probably greater stigma and possibly psychological distress associated with genital herpes, which is a sexually transmitted disease. On the other hand oral herpes is more visible and clustering of blisters around the mouth and face could well be a source of considerable distress in particular for young people (who are generally more self conscious and highly concerned about issues associated with appearance). Genital herpes may be associated with either HSV1 or HSV-2 infection. A probable reason for the concentration on genital herpes in the literature is that these studies are commonly carried out at clinics. Sufferers of non-genital herpes do not frequently attend clinics and therefore obtaining a sample is more difficult. It is important to note that the selection of subjects via clinics is another potential source of bias in these studies.

5.10 The Concept of Stress and the Issue of Negative Affect

Although the concept of stress and the issue of negative affect was discussed in the introductory chapter, it is worth raising these issues again in relation to the research on HSV. More of the studies in the review by Shah and Button (1998) describing HSV recurrence in humans concentrate on the concept of stress as a cause for recurrence. The focus tends to be on negative life events (i.e. objective discrete events such as job loss or bereavement) or self reports of cumulative stressful events (e.g. hassles), although a few do take perceived stress into consideration; even fewer studies in this review have taken depression and mood into consideration.

Evidence of a relationship with HSV recurrence was found to be generally stronger for studies using subjective evaluation of stress rather than only measures of objective events. This is consistent with the emphasis on the subjective components of stress including the appraisal processes (Lazarus & Folkman, 1984) previously mentioned. Psychological factors such as personality characteristics, coping skills and social support may be related to stress appraisal, which in turn may be related to both psychological and physiological consequences. Scores on cumulative events and psychological

distress measures may be influenced by stable personality characteristics such as negative affect or neuroticism rather than impact of environmental stressors (Watson& Pennebaker, 1989). This is an important methodological consideration in research using self reported measures of psychological distress and illness. A further important weakness in studies of this kind is the failure to control for negative affectivity or neuroticism when investigating a relationship between self reported stress and illness.

Levenson (1987) found that depression, anxiety and somatization were associated with symptoms of pain and itching. Stout and Blook (1986) found lower levels of depression, anxiety, isolation and preoccupation with health concerns were associated with fewer recurrences. These findings, however, could be attributed to the effect of negative affect on symptom perception and health concerns. It is important that future studies control for negative affect when evaluating the relationship between psychosocial factors and herpes recurrence.

5.11 Severity and Frequency of Recurrence of HSV

One study which did take severity and frequency of recurrence into consideration was carried out by Silver and colleagues (Silver, Auerbach, Vishnaivsky & Kaplowitz, 1986) who found that emotional dysfunction was higher in patients compared to controls and the *duration* of recurrence was associated with increased levels of stress (i.e. negative life events). High rates of recurrence were associated with having an external locus of control. Lack of cognitive strategies in coping with the stress associated with herpes was found to be associated with more frequent *and* painful recurrences. They did not report on any differences between subjects with high rates of recurrence in relation to those with lower rates of recurrence. Furthermore, these were all retrospective studies, based on participants retrospectively reporting stressful life events/psychological factors and HSV recurrence; again this was a study of genital herpes. Furthermore, 21 of the 66 participants reported suffering a recurrence at the time of the evaluation but were not excluded from the analysis. Suffering from an outbreak of the illness at the time of responding to

the questionnaires could influence their responses to self report measures, in particular retrospective reports of life events and frequency of recurrence.

Hoon (1986) suggested that the construct 'illness vulnerability' (i.e. the number of illnesses in the six months prior to the study) is a central mediator of HSV recurrence. Hoon suggests that stress affects illness vulnerability which in turn affects recurrence rate. The issue of illness vulnerability has not, however, been considered in these studies. An understanding of the relationship between psychological factors and herpes recurrence should take into consideration both current and previous illness as an important factor potentially influencing recurrence.

Vanderplate, Aral and Magder (1988) reported no relationship between self reported stressful recent events or anxiety scores and recurrences over the previous year, however, high appraisal of stress through global self rating was associated with more frequent recurrences.

5.12 Summary

Whilst there is evidence from these studies indicating an association between psychological stress and/or depression and the recurrence of HSV there are also significant methodological problems and issues. These are summarised below.

1. The focus on sexually transmitted genital herpes rather than facial herpes.
   There is a very heavy bias in the literature towards studying the former and whilst the symptoms of both may be very similar, the location of the virus may be an important issue in relation to psychological issues.

2. The issue of sample bias.
   A common feature of these studies is that participants in studies of genital herpes are taken largely from those attending either Genito-Urinary Medicine (GUM) clinics for treatment or seeking help for psychological difficulties associated with genital herpes. This indicates that they are

seeking help for psychological problems associated with the disease or that they are currently suffering from a recurrence (i.e. at the time of the study). This is not the case for oral herpes because largely sufferers of the latter do not attend clinics for treatment.

3. Negative Affect

   Failure to take into consideration negative affect in studies using self report measures, which has been shown to affect respondents' self reported symptoms and questionnaire responses.

4. Previous Illness

   Effect of previous illness (i.e. illness vulnerability). The effect of previous illness should also be taken into consideration as well as the effect of any current illness.

5. Frequency and Severity of Recurrence

   It is important to consider not only the *occurrence* of herpes but the frequency and severity of recurrence.

6. Objective and Subjective measures of Stress

   The need to consider both objective stress and subjective appraisal of stressors and to include other measures of 'enduring psychosocial characteristics' which may be implicated in the ongoing interaction between stress and illness.

7. The role of health risk behaviours and immunosuppression

   The nature of health behaviours; the possible confounding influence of smoking, alcohol consumption, diet, sleep and exercise must be carefully considered in any understanding of psychological stress and illness. As discussed earlier, these health risk behaviours are commonly associated with psychological stress and may in themselves influence both the immune system and immune related illness. There is considerable evidence for the immunosuppressive effects of the lack of sleep, poor nutrition, alcohol consumption and cigarette smoking (e.g. Borysenko &

Borysenko 1982) and the immunoenhancing effect of regular exercise, though excessive exercise may have the opposite effect If, for example, people respond to stress by smoking more or drinking more alcohol then it may be the health behaviours and not the stress itself which is increasing vulnerability to recurrence of herpes simplex.

8. Retrospective vs. Prospective Studies

The nature of retrospective studies means it is unclear whether psychological processes precede HSV recurrences; it is possible that self report of previous events is subject to memory bias. Retrospective and cross-sectional studies tell us little about the temporal relationship between stressors/depression and HSV recurrence, and it is plausible that the recurrence of this disease could be a significant source of anxiety and distress. These issues will be addressed in studies two and three.

There is a need therefore for an investigation of oral/facial HSV and its relationship with psychosocial variables, taking into consideration the numerous methodological issues outlined above.

The following studies investigated the role of psychological factors in the recurrence of HSV.

The first study investigated the relationship between psychosocial factors and oral herpes infection in a cross-sectional analysis which takes into consideration some of the methodological issues discussed above.

Study One is a cross-sectional investigation of the differences between those who suffer from herpes and those who do not, on a range of psychosocial measures of stress and psychological well being.

Study Two is a longitudinal diary study investigating the role of stress and depression as contributory factors in the recurrence of HSV infectious outbreak.

Study One is reported in the next chapter.

CHAPTER 6

6.1 Study One

A Cross Sectional Investigation Of The Role Of Psychosocial Factors In A Sample Of Participants Currently Suffering Recurrences Of Herpes Simplex Compared With A Sample Of Participants Free From This Virus.

The following are a list of aims which this study set out to achieve.

6.2 Aims

1. To compare the participants suffering recurring oral/facial herpes virus infections (i.e. cold sore group) and participants free from HSV infections (i.e. control group) on demographics and general health and medical background including previous illness, current health, frequency of infectious illness and medication use
2. To compare the cold sore group and the control group on a range of health risk behaviours such as diet, exercise, smoking and alcohol
3. To describe the clinical picture of a cold sore recurrence as well as the sufferers' experience of the illness (i.e. frequency and severity of recurrence, factors felt to precipitate a recurrence)
4. To investigate, cross-sectionally, differences between the cold sore group and the control group on measures of stress (both objective and subjective) and stable psychological characteristics
5. To investigate differences between the group on coping strategies and social support
6. To investigate differences between the groups on symptoms, cognitive difficulty and emotional well being
7. To investigate the possible confounding effects of negative affect and previous illness in the relationship between stress and cold sore recurrence

8. To investigate the relationship between frequency of cold sore recurrence in the previous year and frequency of other infectious illness
9. To consider the issue of illness chronicity by comparing those suffering frequent recurrences of oral herpes with those suffering fewer recurrences. To re-analyse differences between the groups taking into consideration the possible confounding effects of both negative affect and previous illness

The first two aims were to ensure that the control group and the cold sore group were matched on important variables that could bias the findings and to highlight any important medical or health risk behaviours that might distinguish the two groups

6.3 Method

6.3.1 Participants

All volunteers were students studying at the University of Glamorgan. The total number of students who completed the study was 38. There were twenty participants in the cold sore group and 18 in the control group. As discussed earlier, recruitment of participants suffering from particular illnesses is always difficult when not recruiting directly from a clinic or hospital. Whilst it is desirable to study larger numbers when possible, it was felt that 20 cold sore participants (with a similar number in the control group) would be a suitable number for the design of this study.

The following table gives a breakdown of the participants' age, gender, marital and work status.

Table 19. Demographic information on the Cold sore Participants and the Control group

	cold sore group	control group
Gender:	Males n = 2 Females n = 18	Males n= 3 Females n= 15
Age:	mean = 27.6 range = 19-52	mean = 25.3 range = 19-40
Marital Status:	3 married 14 single 4 divorced	7 married 9 single 1divorced 1 widowed
Work status	5 employed 15 not employed	10 employed 8 not employed

6.3.2 Background and Recruitment of Volunteers

Participants were recruited via a leafleting campaign at the University of Glamorgan. Leaflets were handed out to students in five large lectures (approximately 700 students). Participants were required to indicate on a form:

a) whether they had ever suffered from cold sores

b) whether they were currently suffering from cold sores and if so the frequency of recurrence

c) when they last had a cold sore

d) whether they would be willing to participate in a study of cold sores and finally their name and telephone number (or email address) for contacting.

6.3.3 Cold Sore Group

Respondents were followed up on the basis that they were currently suffering from episodes of cold sores (i.e. that they had had at least one recurrence in the past 6 months). Those who had suffered from cold sores but who did not have recent recurrences (i.e. a recurrence within the last 12 months) were excluded from the study. It was anticipated that this would increase the likelihood that participants in the study would have a recurrence of the virus during the diary period. Participants were contacted by telephone and/or email and an appointment was made for them to come and discuss the possibility of taking part in the study. Those who agreed to participate were given a further appointment to come in and complete the questionnaires containing the psychosocial measures and to be given the diaries for completion on a weekly basis. Participants were paid £10 for completion of the study.

6.3.4 Controls

The control group consisted of a matched sample of students who did not suffer from cold sores and were selected from the respondents and asked to participate in the study.

6.3.5 Procedure

All participants who met the inclusion criteria were given an appointment to come in and complete the questionnaires as described above. The booklets took approximately 20 minutes to complete. Participants were assured of the confidentiality of the information they provided.

6.3.6 Baseline Questionnaire Measures (see Appendix A2.2,A2.3)

The questionnaire was similar to the one used in the Glandular Fever Study. Section One (measuring socio-demographic variables & medical history/general health) and Section Two (measuring health behaviours) was the same.

6.3.7 Clinical Picture

This section of the questionnaire and was designed to collect information from Cold sore sufferers only. They were required to provide information regarding their cold sore infections. The history of the illness including length of time since first episode, the frequency of recurrence, the general severity of episodes and the severity of the previous episode, and the types of treatment they used for their cold sores.

6.3.8 Measures of Stress and Psychosocial Factors

The same, standard, psychosocial measures that were used in the Glandular Fever Study were used in this study and are fully described in Chapter Two. The psychosocial measures, in summary, used in this study were:

1. The Life Events Scale (Henderson, Byrne and Duncan-Jones (1981) measuring positive and negative major life events in the past twelve months and their impact.
2. Daily Hassles (frequency, cumulative severity and intensity) were measured using the Hassles Scale developed by Kanner, Coyne, Schaefer and Lazarus (1981).
3. The Perceived Stress Scale (Cohen, Kamarch & Mermelstein, 1983) to measure the degree to which situations in one's life are appraised as stressful.
4. The Beck Depression Inventory (Beck et al., 1961, 1988); measuring cognitive and physical symptoms of depression.
5. The Positive and Negative Mood Scale (Zevon and Tellegen (1982); measuring mood by a list of adjectives.
6. The LOT measure of Dispositional Optimism (Scheier & Carver, 1987); measuring optimism or pessimism.

7. Measure of Trait Anxiety (Spielberger et al., 1970); A measure of negative affectivity.
8. Multidimensional Health Locus of Control Scale (Wallston et al., 1976, 1978 measuring 3 dimensions of health locus of control beliefs (i.e. internal, powerful others and chance externality)
9. Self Esteem Scale. (Social confidence & Self Regard – adapted from Fleming & Watts, 1980).
10. Coping Strategies: The Ways of Coping Questionnaire (Folkman and Lazarus, 1980 and 1988). Categorised as (a) problem solving, (b) confrontative coping, (c) positive adjustment, (d) seeking social support, (e) escape avoidance and f. distancing.
11. The ISEL Social Support Scale. (Cohen & Hoberman, 1983); categorised as of (a) appraisal, (b) belonging, (c) self esteem, and (d) tangible support.
12. The Profile of Fatigue Related symptoms (Ray et al., 1992); Responses are scored according to the following four categories: (a) cognitive difficulty, (b) somatic symptoms, (c) fatigue, and (d) emotional distress.

6.4 Results

The results are organised to address the Aims outlined earlier.

Section 1 addresses Aims 1 and 2, comparing the herpes group and the healthy control group on health, recurrence of infectious illness, and health behaviours.

Section 2 addresses Aim 3 reporting on the clinical picture of HSV, frequency and severity of recurrence.

Section 3 addresses Aim 4, 5 and 6 comparing the herpes group and the healthy controls on psychosocial measures.

Section 4 addresses Aim 7 to reanalyse the psychosocial measures controlling for negative affectivity .

Section 5 addresses Aim 8 investigating frequency of cold sore recurrence in previous year and the frequency of other infectious illness (and the confounding effect of previous illness).

Section 6 addresses the issue of frequency of cold sore recurrence and compares high recurrence and low recurrence groups, co-varying negative affect and previous illness.

6.5 Section 1: Comparison of Control Group and Herpes Group on Measures of General Health and Health Behaviours

The cold sore group and the control group were well matched on demographic variables (see Table 18). They were all University Students at the same Institution with a similar age range although the control group were very slightly younger on average. The gender bias was towards females but this bias was the same in both the groups. Slightly more participants in the control groups had part time jobs outside college but this was not significant.

The groups were compared on measures of general health and medical history. There were no significant differences between the cold sore participants and the healthy control participants on a range of measure of general health, other medical conditions, allergies or the use of prescribed drugs. The cold sore group overall were more likely to use over the counter

drugs ($P<0.01$) and vitamins ($P<0.01$). A table of differences in current health is shown in Appendix 3.8.

In this study the participants were well matched on health behaviours; the groups indicated similar levels of healthy eating and consumption of healthy and non healthy food. There were few smokers overall and little difference between the cold sore (3 smokers) and non cold sore (4 smokers) groups. There were no differences between the groups in the average number of hours slept per night, although the quality of the sleep was somewhat impaired for the cold sore group compared with the control group.

Although there were no significant differences in alcohol consumption between the control group and the cold sore participants there was a tendency for the cold sore group to indicate more moderate drinking. A table showing the amount of alcohol consumed by the Cold sore Participants and the Healthy Controls can be seen in Appendix 3.9.

The groups were compared on exercise and again the groups participated in similar levels of energetic and less energetic sport. A table showing the comparison between the groups on participation in exercise is shown in Appendix 3.9.

Overall, there was a high level of consistency between the groups on the range of health behaviours measured in this study.

6.6 Frequency of Colds and Infectious Illness

There was a tendency for the cold sore group to have suffered more frequent colds in the past 12 months - 35% of the cold sores group reported very few colds compared with 72% of the control group; 25% of the cold sore group suffered a lot of colds in the past 12 months compared with only 6% of the control group. The cold sore group also suffered more sore throats and more bouts of influenza in the past twelve months than the control group. These data are shown in the Table below. There were no differences between the

groups in the incidence of bronchitis or other illness which suggests that differences relate to susceptibility to upper respiratory tract infections and not to illness reporting in general.

Table 20: Occurrence of colds, flu and upper respiratory tract infections in the last 12 months in cold sore group and control group

	Not at all		Very few		Average		A lot	
	Cold sores	Healthy	Cold sores	Healthy	Cold sores	Healthy	Cold sores	Healthy
Colds	1 (5%)	0	7 (35%)	13 (72%)	7 (35%)	4 (22%)	5 (25%)	1 (6%)
Sore Throat	4 (20%)	5 (28%)	6 (30%)	9 (50%)	8 (40%)	2 (11%)	2 (10%)	2 (11%)
Flu	9 (45%)	13 (72%)	6 (30%)	5 (28%)	4 (20%)	0	1 (5%)	

6.7 Section 2: History of HSV Infection (experimental group only)

The length of time since first infection ranged from one month to twenty years ago. The mean number of episodes per year was 4.5 with most participants having either two or five episodes a year. The range was from 1 per year to 24. 4 of the cold sore sufferers (20%) were currently suffering from a recurrence. Only 35% of the participants had ever seen a Doctor about their cold sores. 78% of the cold sore group reported that they use Zovirax as the preferred form of treatment. The average severity of the last recurrence was 2.3 where 0 is mild and 5 is extremely severe. The mean severity in general was reported to be 2.75. The table below shows the range of reported severity scores for the cold sore group for both the previous episode of a cold sore and the general level of severity.

Table 21: Reported Severity of cold sores episodes

Level Of Severity	Mild 0	1	2	3	4	Extremely Severe 5
Last episode	(1) 5%	(6)30%	(6) 30%	(3)15%	(1)5%	3 15%
Severity in general	(1) 5%	(1) 5%	(6) 30%	(7)35%	(4)20%	(1) 5%

Cold sore participants were asked to report on the impact of having a cold sore. 70% of the sample indicated that the illness had a moderately negative impact on their lives. They were also asked to rate the importance of factors influencing recurrence on a scale ranging from 1 not important to 5 extremely important. The next table shows what factors the cold sore sufferers perceived a range of factors to be on the development of a cold sore i.e. how important each factor was in terms of the recurrence of a cold sore episode.

Table 22: Factors reported by herpes sufferers to influence recurrence of cold sore

Range of Scores =	Not important 1	2	3	4	Extremely important 5	Mean
Lack of sleep	(2) 10%	(6) 30%	(6) 30%	(4) 20%	(2) 10%	**2.9**
Poor general health	(5) 25%	0	(2) 10%	(8) 40%	(5) 25%	**3.4**
Other Infections (colds etc.)	(1) 5%	(1) 5%	(4) 20%	(5) 25%	(9) 45%	**4.0**
Poor diet/eating badly	(3) 15%	(6) 30%	(8) 40%	0	(3) 15%	**2.7**
Too much alcohol	(8) 40%	(7) 35%	(3) 15%	(1) 5%	(1) 5%	**2.0**
Menstruation	(11) 55%	(4) 20%	(2) 10%	(2) 10%	(1) 5%	**1.9**
U.V.sunlight	(3) 15%	(5) 25%	(3) 15%	(4) 20%	(5) 25%	**3.2**
Stress	(2) 10%	0	(1) 5%	(6) 30%	(11) 55%	**4.2**

6.8 Summary and Discussion of History of HSV Infection

This is largely self explanatory. It can be seen that the time since primary infection ranged from one month to twenty years. Most of the participants were either two years or five years since their primary infection. There was a wide range in the frequency of recurrences over a year with most having on average one or two episodes per year, although one subject reported having twenty four episodes a year. Most use Zovirax to treat the infection which they report to be effective in limiting the severity of the episode. In terms of the importance of precipitating factors, it can be seen that (a) stress followed by (b) other infections were reported to be the most important factors influencing the onset of an episode.

6.9 Section 3: Analysis of Stable Psychosocial Measures taken at Time One

Correlations to show associations between the variables are shown in Appendix A3.10. One-way ANOVAs were calculated to analyse the differences between the cold sore group and the control group on a range of standard measures of stress and psychosocial factors at baseline. 4 of the cold sore participants were suffering an episode of cold sore at base line and these participants were removed from the analysis so that all those in the cold sore group were cold sore free at the time of testing. One of the participants in the healthy control group who was currently suffering a recurrence of a chronic, recurring illness was also removed from the analysis; this left 17 participants in the healthy control group and 16 participants in the cold sore group.

The series of tables reported below show differences between the groups on the baseline psychosocial measures.

Table 23: Mean Scores (sd) for Healthy Group and Cold Sore group on psychosocial stress measures

Measure	Healthy group Mean (s.d.)	Cold sore group Mean (s.d.)	Significance
Perceived Stress	15.77 (5.76)	23.69 (7.25)	Sig. P = 0.001
Total life events	2.24 (2.36)	3.88 (2.39)	Sig. P = 0.05
Minor daily hassles: Frequency	8.88 (6.63)	30.12 (25.67)	Sig. P = 0.002
Cumulative Severity	13.82 (12.14)	55.75 (57.66)	Sig. P = 0.005
Intensity	1.49 (0.5)	1.65 (0.8)	ns

6.10 Summary of findings from Cross-Sectional Analysis

The cold sore group experienced significantly more life events over the past twelve months; they also suffered from more frequent and more severe daily hassles than the healthy group. Although the cold sore group were suffering significantly more from these stressors, the impact of these stressors may be mediated by the cognitive appraisal of those events; the next measure of stress takes into consideration differences between the groups in perceived stress. The table above shows that the cold sore group did, in fact, score significantly higher on perceived stress (i.e. the perception that events in their lives were unpredictable, uncontrollable and overloading).

Table 24: Mean Scores (sd) for Healthy Group and Cold Sore group on measures of mood and personality

Measure	Healthy group Mean (s.d.)	Cold sore group Mean (s.d.)	Significance
Depression	3.88 (1.90)	9.5 (4.61)	Sig. P = 0.0000
Trait Anxiety	34.0 (5.76)	45.81 (5.81)	Sig. P = 0.0001
Positive mood	37.53 (7.83)	30.69 (12.64)	Sig. P = 0.06
Negative mood	10.58 (7.62)	18.10 (9.67)	Sig. P = 0.01
Self Esteem	61.53 (10.49)	48.53 (10.75)	Sig. P = 0.001
Optimism	36.12 (5.95)	26.81 (5.27)	Sig. P = 0.0000

The cold sore group were significantly more depressed and were higher in negative mood (lower in positive mood) than the control group. They experienced a significantly higher level of trait anxiety than the control group, and were lower on the personality measures of dispositional optimism and self esteem.

Table 25: Mean Scores (sd) for Healthy Group and Cold Sore group on Profile of Fatigue Related Symptoms

Measure	Healthy group Mean (s.d.)	Cold sore group Mean (s.d.)	Significance
Fatigue Related Symptoms: Emotional Difficulties	20.71 (8.6)	41.44 (21.43)	Sig. P = 0.0009
Fatigue	15.53 (7.57)	29.13 (16.25)	Sig. P = 0.004
Cognitive Difficulties	14.29 (3.84)	31.31 (17.26)	Sig. P = 0.0004
Somatic Symptoms	21.24 (6.01)	37.56 (18.84)	Sig. P = 0.001

Again, it can be seen from this analysis that the cold sore group were significantly higher than the control group on the measures of cognitive and emotional difficulty, somatic symptoms and fatigue.

Table 26: Mean Scores (sd) for Healthy Group and Cold Sore group on Social Support and Coping Strategies

Measure	Healthy group Mean (s.d.)	Cold sore group Mean (s.d.)	Significance
Social Support: ISEL S	31.64 (2.71)	28.62 (2.88)	Sig. P = 0.003
ISEL B	35.0 (3.46)	30.43 (4.6)	Sig. P = 0.002
TOTAL ISEL	127.19 (5.88)	116.56 (12.14)	Sig. P = 0.004
Coping Strategies: positive readjustment	10.88 (2.29)	13.69 (4.09)	Sig. P = 0.02
accept responsibility	6.35 (1.97)	9.25 (3.19)	Sig. P=0.003
self control	12.88 (3.22)	15.94 (4.19)	Sig. P = 0.02
escape avoidance	10.41 (2.72)	16.06 (5.43)	Sig. P = 0.0006
Distancing	8.41 (2.5)	13.44 (4.31)	Sig. P = 0.0003

Whilst most of the social support sub-scales did not show any significant differences between the cold sore group and the healthy group, there were significant differences in the subscales of (a) 'self-esteem social support' (ISEL S), this is described as 'the perceived availability of positive comparisons when comparing oneself to others' and (b) on 'belonging social support' (ISEL B) which is the perceived availability of people one can do things with. The overall score for social support was significantly lower in the cold sore group.

There were some significant differences in the coping strategies used by the cold sore group who used significantly more positive readjustment (mean = 10.88 vs. 13.69); accepting responsibility (6.35 vs. 9.25); self control (12.88 vs. 15.94); escape avoidance (10.41 vs. 16.06); and distancing (8.41 vs. 13.44). The cold sore group appeared to use more of both cognitive approach strategies as well as denial avoidance strategies.

6.11 Section 4: The Role of Negative Affect

Although it would appear from this analysis that people who are suffering from recurring HSV are suffering from more stress, anxiety and depression than those who are free from such viruses, before this conclusion can be reached, possible confounding variables need to be taken into consideration. These results support the findings of much previous research investigating the relationship between stress and illness, but an important omission in much of this research, as discussed in both the introduction and in the glandular fever study, is the fact that no control is made for the role of negative affect. As discussed earlier it is possible that the high scores on the psychosocial measures may be due to this tendency of highly anxious individuals to score higher on these psychosocial measures

6.12 Re-analysis Of differences between Cold Sore and Control Groups on Psychosocial Measures at Baseline Controlling for Negative Affect

The following set of tables report the results of ANOVAS and ANCOVAS to investigate whether differences in psychosocial measures are maintained when negative affect is co-varied.

Table 27: Difference between the cold sore and healthy groups on measures of psychosocial stress controlling for negative affect

Psychosocial Variable	Healthy Control Group N=17	Cold sore Group N=16	Sig.
Perceived Stress	15.76	23.69	
Co-vary trait anx	19.52	19.69	n.s.
Negative Life Events	1.06	2.18	
Co-vary trait anx.	1.54	1.67	n.s.
Total Life Events	2.24	3.88	
Co-vary trait anx.	2.73	3.35	n.s.
Hassles-cum. sev	13.82	55.75	
Co-vary trait anx.	25.15	43.71	n.s.(0.28)
Hassles-frequency	8.88	30.12	
Co-vary trait anx.	13.36	25.36	n.s.(0.14)
Hassles-intensity	1.49	1.65	
Co-vary trait anx.	1.65	1.47	n.s.(0.28)

There were no significant differences between the groups on measures of Perceived Stress, Negative and Total life events and Minor Daily Hassles, when negative affect was co-varied.

Table 28: Difference between cold sore group and control group on measures of depression, mood and personality controlling for negative affect

Psychosocial Variable	Healthy Subjects N=17	Cold sore Subjects N=16	Sig.
B.D.I.	3.88	9.50	
Co-vary trait anx.	4.91	7.34	0.02
Negative Mood	10.58	18.06	
Co-vary trait anx.	15.41	12.94	n.s.
Self Esteem	61.53	48.53	
Co-vary trait anx.	55.44	55.43	n.s.
Life Orientation	35.11	26.81	
Co-vary trait anx.	32.25	30.02	n.s.

There were no differences between the groups on negative mood, self esteem, life orientation, fatigue, emotional and cognitive difficulty, somatic symptoms or social support when negative affect was co-varied. The differences between the cold sore group and the healthy controls in depression remained significant.

Table 29: Difference between the cold sore group and the control group on fatigue, emotional difficulty, cognitive difficulty, somatic symptoms and social support

Psychosocial Variable	Healthy Subjects N=17	Cold sore Subjects N=16	Sig.
Fatigue	15.53	29.12	
Co-vary trait anx.	21.73	22.53	n.s.
Emotional Difficulty	20.71	41.43	
Co-vary trait anx.	34.85	29.66	n.s.
Cognitive Difficulty	14.29	31.31	
Co-vary trait anx.	19.24	26.06	n.s (0.15)
Somatic Symptoms	21.24	37.56	
Co-vary trait anx.	28.10	30.26	n.s.
Total Social Support	127.18	116.58	
Co-vary trait anx.	123.21	120.48	n.s.

Again, there were no significant differences between the groups when negative affect was co-varied.

6.13 Summary

The large differences in the standard psychosocial measures between the cold sore group and the control group were no longer significant when trait anxiety was co-varied. The only measure which remained significantly different between the groups, after co-varying negative affect was depression; the cold sore group continued to score significantly higher on the BDI than the control group after co-varying negative affect. The large differences between healthy controls and the illness group on measures of psychosocial well being may be a consequence of those who are highly anxious perceiving more illness and scoring higher on self reports of psychosocial well being.

6.14 Section 5: Frequency of Illness Recurrence

The next two issues addressed in the analysis are: a. the issue of frequency of recurrences of cold sores. and b. the possible confounding effects of previous illness. In the review of studies of HSV, it was suggested that the issue of illness chronicity (i.e. those suffering frequent recurrences of the illness) may be an important factor. The large differences in how often people suffer from recurrences needs to be taken into consideration. The question addressed here was whether there were significant differences in psychosocial measures between those suffering frequent recurrences of cold sores than those suffering few recurrences. The next series of analysis addresses this question as well as considering the role of frequency of previous illness in general.

6.15 Frequency of previous illness

This issue was raised in the literature review in terms of 'illness vulnerability', where Hoon (1986) noted that the number of illness suffered in the past twelve months may be a mediator of HSV recurrence. In this study, the frequency of previous illness in the last twelve months was taken into consideration in the next set of analysis.

6.16 Analysis of the Frequency of Recurrence of Cold Sores and Psychosocial Variables

The cold sore group were divided into those having two or more recurrences of cold sore in the previous year and those having only one or less recurrence (this was based on a median split). The three groups in the next set of analyses were the healthy controls compared with the low incidence of cold sore group and the high incidence of cold sore group. These groups were firstly considered in relation to frequency of *other* infectious illness.

6.17 Effect of other infectious illness in the past twelve months

The incidence of other infectious illness was compared for the three groups and an ANOVA was carried out to measure the differences between the groups. The following table shows differences between the groups in previous illness, co-varying negative affect.

Table 30: Mean Scores (sd) for the high incidence and low incidence cold sore participants and the healthy control group on frequency previous illness, co-varying negative affect

	Non Cold sore Mean (sd)	Cold sore low incidence Mean (sd)	Cold sore high incidence Mean (sd)	Sig.
Previous Illness	7.6** (1.6)	7.9 (1.9)	10.6** (2.7)	0.009
Co-vary Trait anxiety	7.8* (0.56)	7.8 (0.82)	10.1* (0.65)	0.04

The above table shows that there were significant differences between the high incidence cold sore group and the healthy control on the frequency of previous illness.

This difference was maintained when negative affect was co-varied.
The difference was not significant for the low incidence cold sore group who were very similar to the healthy controls in frequency of previous illness.
(See Appendix A.312 for previous illness in the healthy control group).

6.18 Within the Cold Sore Group only, Participants were divided by the number of Illnesses (other than cold sores) in the previous 12 months

ANOVAs were calculated to measure differences in psychosocial factors between those who had suffered a lot of previous other illnesses compared with those who had suffered little previous illness. Those who suffered more illness in the previous 12 months did not score significantly higher on standard psychosocial measures of perceived stress, depression, mood etc. than those who suffered less illness. Those who suffered more illness in the previous 12 months did report a significantly greater number of negative life events and used coping strategies relying on confrontation and problem solving. Generally, however, there was little effect of previous illness on psychosocial measures in the cold sore group.

Those who suffered from a greater number of recurrences of cold sores in the past twelve months were also more vulnerable to the development of more frequent viral infections, largely colds and influenza. This group are high on psychosocial measures of stress and depression however this relationship is not simply a consequence of negative affect (as measured by trait anxiety) influencing their responses to questionnaires or the perceived severity of their illness. The differences between those suffering frequent recurrence of cold sores and the healthy controls was significant even when trait anxiety and previous illness were co-varied. So, it does not appear that previous illness is the important factor influencing levels of psychosocial stress and depression and the subsequent development of illness. Those who subsequently suffer more illness (i.e. the high frequency cold sore group) do so independently of their previous illness levels.

6.19 Summary

The high incidence cold sore group were significantly more likely to have a higher incidence of other illnesses than the control group. They also tended to have more illness than the low incidence cold sore group. This relationship between higher incidence of previous illness and frequent recurrence of cold sore remained significant even when trait anxiety was controlled. The low incidence cold sore recurrence group were very similar to the control group in terms of frequency of suffering from other infectious illness. This supported Hoon's notion of illness vulnerability mediating the frequency of cold sore recurrence. This also suggests that the analysis of the relationship between psychosocial factors and cold sore recurrence needs to control for previous illness.

The next analysis controls for both negative affect and previous other illness. Anovas were calculated to measure the overall differences between the control group and the high incidence and low incidence cold sore group on the range of psychosocial measures discussed. Post hoc analyses were conducted to indicate how the groups differed from each other.

Table 31: Mean Scores (sd) for the high and low incidence cold sore and control groups on psychosocial measures (Perceived Stress, Life Events and Hassles) controlling for negative affect and previous other illness

Measure & Significance	3. Non-cold sore group N=17 Mean (sd)	2. Cold sores – Low incidence N=7 Mean (sd)	1. Cold sores – High Incidence N=13 Mean (sd)	Post-hoc differences Between the groups
Perceived Stress ***	15.8 (5.8)	19.9 (8.3)	26.7 (5.5)	1 & 3 **
Covary prev. illness ***	15.8 (1.4)	19.9 (2.2)	28.2 (1.2)	1 & 2 *
Covary NA***	19.71.2)	17.8 (1.6)	24.2 (1.3)	
Negative Life Events *	1.1 (1.7)	1.3 (1.3)	2.9 (1.7)	1 & 3*
Covary Prev. Illness *	1.3 (0.3)	1.5 (0.6)	2.9 (0.5)	
Covary NA*	1.5 (0.4)	1.1 (0.6)	2.9 (0.5)	
Total Life Events *	2.2 (2.4)	2.6 (1.4)	4.9 (2.2)	1 & 3*
Covary Prev. Illness *	2.5 (0.5)	2.9 (0.8)	4.4 (1.6)	
Covary NA *	2.6 (0.6)	2.4 (0.8)	4.7 (0.7)	
Hassles – Cum.Severity ***	13.8 (12.1)	30.3 (42.4)	75.6 (52.5)	1 & 3 ** 1 & 2 *
Covary Prev. Illness **	15.2 (9.4)	31.6 (14.3)	63.3 (11.3)	
Covary NA*	24.2 (9.9)	24.7 (13.6)	55.1 (11.1)	
Frequency ***	8.9 (6.6)	16.9 (16.8)	40.4 (23.4)	1 & 3 **
Covary Prev. Illness ***	10.0 (4.1)	17.9 (6.2)	34.2 (4.9)	1 & 2 *
Co-Vary NA **	12.8 (4.5)	14.8 (6.1)	32.3 (4.9)	

* = $p<0.05$ ** $p<0.01$ *** $P<0.001$

Highly significant differences between the groups on measures of perceived stress, negative life events and hassles remained significant even when negative affect and previous illness were controlled. The effects were due largely to the high frequency group being significantly different from the control group, which accounts for the fact that the previous analysis showed no difference between the control group and the cold sore group as a whole.

Table 32: Mean Scores (sd) for the high and low incidence cold sore and control groups on psychosocial measures (depression, mood and personality) controlling for negative affect and previous other illness

Measure & Significance	3. Non-cold sore group N=17 Mean (sd)	2. Cold sores – Low incidence N=7 Mean (sd)	1. Cold sores – High Incidence N=13 Mean (sd)	Post-hoc differences Between the groups
B.D.I. ***	2.9 (1.9)	8.3 (4.2)	10.4 (4.7)	
Covary Prev. Illness ***	2.9 (0.9)	8.29 (1.4)	9.9 (1.1)	1 & 3 ** 2 & 3 *
Covary NA*	5.2 (0.6)	7.0 (0.9)	7.6 (0.7)	
Negative Mood ***	10.6 (7.6)	13.0 (8.5)	22.0 (8.3)	
Covary Prev.Illness *	10.8 (2.1)	13.2 (3.1)	20.5 (2.5)	1 & 3 ** 1 & 2 *
Covary NA*	10.3 (2.4)	15.6 (1.6)	15.7 (1.7)	2 & 3 *
Self Esteem **	61.5 (10.5)	52.00 (11.5)	46.22 (9.3)	
Covary Prev. Illness *	60.8 (2.6)	50.9 (4.3)	49.6 (3.1)	1 & 3 **
Covary NA ns	55.1 (2.1)	56.8 (3.1)	54.3 (2.3)	
Life Orientation ***	36.1 (6.0)	26.3 (5.6)	27.2 (5.0)	
Covary Prev. Illness ***	35.7 (1.4)	25.9 (1.1)	27.7 (1.1)	1 & 3 ** 2 & 3 **
Covary NA*	33.2 (1.2)	27.9 (1.7)	29.9 (1.4)	

* = p<0.05 ** p<0.01 *** P<0.001

It can be seen that depression continues to be significantly higher in the cold sore group when co-varying previous illness; however, the difference does not quite reach significance when NAis co-varied. Negative mood continues to be important for the frequent recurrence cold sore group as does Life Orientation.

Table 33: Mean Scores (sd) for the high and low incidence cold sore and control groups on psychosocial measures (Profile of Fatigue Related Symptoms) controlling for negative affect and previous other illness

Measure & Significance	3. Non-cold sore group N=17	2. Cold sores – Low incidence N=7	1. Cold sores – High Incidence N=9	Post-hoc differences Between the groups
Emotional Difficulty ***	20.7 (8.6)	32.7 (16.9)	48.2 (19.5)	
Covary prev. illness ***	21.1 (3.8)	33.0 (5.7)	46.5 (4.5)	1 & 3 **
Covary NA *	31.0 (2.4)	27.2 (3.3)	36.7 (2.7)	
Fatigue ***	15.5 (7.6)	25.0 (13.1)	32.3 (15.3)	
Covary Prev. Illness **	15.8 (3.0)	25.3 (4.6)	31.1 (3.6)	1 & 3 **
Covary NA ns	21.8 (2.6)	21.6 (3.6)	25.2 (2.9)	
Cognitive Difficulty ***	14.3 (3.8)	23.9 (15.8)	37.1 (15.3)	1 & 3 **
Covary Prev. Illness ***	14.8 (3.0)	24.3 (4.5)	34.2 (3.5)	1 & 2 *
Covary NA *	19.8 (2.8)	20.9 (3.8)	29.5 (3.1)	
Somatic Symptoms **	21.2 (6.0)	32.7 (24.6)	41.3 (11.8)	1 & 3 **
Covary Prev. Illness**	22.1 (3.3)	33.6 (5.0)	40.0 (4.0)	
Covary NA ns	27.8 (3.1)	29.2 (4.2)	34.95 (3.4)	

* = p<0.05 ** p<0.01 *** P<0.001

Differences were between the high frequency cold sore group and the healthy controls, these differences largely remained significant when previous illness was co-varied but did not quite reach significance when negative affect was co-varied although the trend was in the anticipated direction.

Table 34: Mean Scores (sd) for the high and low incidence cold sore and control groups on psychosocial measures (Social Support and Coping strategies) controlling for negative affect and previous other illness

Measure & Significance	3. Non-cold sore group N=17	2. Cold sores – Low incidence N=7	1. Cold sores – High Incidence N=9	Post-hoc differences Between the groups
SOCIAL SUPPORT:				
ISELS ***	31.7 (2.7)	29.3 (2.8)	28.1 (2.7)	
Covary Prev.	31.7 (0.7)	29.4 (1.1)	28.6 (0.8)	
Illness *				1 & 3 **
Covary NA ns	30.5 (0.7)	29.9 (0.9)	29.9 (0.8)	
ISELB **	35.0 (3.1)	31.7(3.0)	29.44 (0.9)	
Covary Prev				
Illness *	34.2 (0.9)	31.2 (1.1)	29.9 (0.7)	
Covary NA ns	33.2 (0.8)	31.1 (0.9)	31.5 (0.8)	1 & 3 **
Total ISEL**	127.2 (5.6)	117.9 (7.0)	115.6 (14.5)	
Covary Prev.				
Illness *	127.0 (2.4)	117.8 (3.8)	116.7 (3.0)	
Covary NA ns	123.6 (2.2)	119.8 (3.8)	120.1 (3.2)	
Coping Strats: Positive Readjustment *	10.9 (2.2)	12.9 (4.7)	14.3 (4.5)	
Covary Prev.				
Illness ns	11.5 (0.8)	13.5 (1.3)	14.6 (1.0)	1 & 3 *
Covary NA ns	11.7 (0.9)	12.4 (1.4)	14.9 (1.1)	
Accept Responsibility **	6.4 (1.9)	9.4 (2.9)	9.1 (3.3)	
Covary Prev.	6.7 (0.7)	9.8 (0.9)	8.3 (0.9)	
Illness *				1 & 3 *
Covary NA ns	7.5 (0.7)	8.8 (0.9)	7.8 (0.9)	
Self Conf. *	12.9 (3.1)	16.7 (5.2)	15.3 (3.6)	
Covary Prev.				
Illness *	13.6 (0.7)	17.4 (1.2)	14.5 (0.9)	1 & 3 *
Covary NA ns	14.0 (0.7)	16.1 (1.4)	14.8 (1.0)	
Escape Avoidance **	10.4 (2.7)	16.0 (5.6)	16.1 (5.5)	
Covary Prev.				
Illness **	11.4 (1.2)	16.7 (1.6)	16.1 (1.3)	1 & 3 *
Covary NA ns	11.8 (91.3)	15.3 (1.6)	16.2 (1.3)	2 & 3 *
Distancing***	8.4 (2.5)	14.6 (4.5)	12.6 (3.5)	
Covary Prev.				1 & 3 *
Illness ***	8.6 (0.8)	14.8 (1.3)	12.3 (1.0)	2 & 3 **
Covary NA **	8.5 (0.9)	14.5 (1.3)	12.6 (1.1	

* = p<0.05 ** p<0.01 *** P<0.001

The differences in social support and coping generally were not significant after controlling for the confounding factors of previous illness and negative affect. The only coping strategy which remained significant after co-varying both previous illness and negative affect was 'distancing'.

6.20 Summary

Differences in the standard psychosocial measures were significant, largely, only for the high incidence cold sore groups and not the low incidence cold sore group. There was a trend for the low incidence group to have somewhat higher scores on most of the measures but this did not generally reach significance apart from on the measures of depression and some of the coping strategies.

It becomes clear from these analyses that those who are experiencing more frequent recurrences of cold sores are the ones who are experiencing: (a) more stress (both objective and perceived); (b) more depression and negative mood; (c) more emotional and cognitive difficulties; and (d) a more pessimistic outlook. These differences remained significant even when the incidence of previous other illnesses was co-varied and, for the most part, they also remained significant when negative affect was taken into consideration.

The higher incidence cold sore group also appear to have a greater vulnerability to the development of other infectious illness, although, as can be seen from the previous analyses, whilst they also scored highly on the psychosocial variables it was not the incidence of previous illness that influenced these high scores because the high scores remained when previous illness was co-varied. These findings could indicate a general immunosuppressive effect of high levels of stress, anxiety and depression leading to greater vulnerability to both illness and recurrence of latent virus.

Alternatively it could be that the high levels of illness resulted in greater stress, that is why it is necessary to study this relationship in a longitudinal study.

The relationship between frequency of recurrence and psychosocial measures appears to be very robust. The critical factor appears to be the chronicity of the illness in terms of the number of recurrences of HSV suffered. The significance of the psychosocial factors (after controlling for important confounding variables) appear to be in relation to this high frequency group. This finding may provide some explanation for the conflicting results in this area of research, discussed earlier. Most of the studies do not take frequency of recurrence into account and therefore variability in results may be a consequence of this. The observation that the relationship between psychological stress and herpes recurrence is less robust in those over 30 years, from Zorilla and colleagues (Zorilla et al., 1996) supports the suggestion that chronicity is an important factor. This is a disease where there are particularly large variations in how much people suffer; in this study alone the range was from one per year to two per month. It seems logical to conceive of those suffering from frequent recurrences of the illness as falling into a category of 'chronically ill' similar in some respects to the glandular fever patients who suffer frequent recurrences of the early symptoms of glandular fever. These chronically ill participants appear to experience higher levels of psychological stress and suffer frequent recurrences of other infectious illness. Evidence from research using a psychoneuroimmunolgy framework would provide an explanation for this finding in terms of high stress, suppressed immune function, recurrence of illness and vulnerability to other circulating common viral infections. The diathesis model of stress would explain the specific vulnerability to a particular illness.

However, these analyses do not clearly indicate any causal relationship between the psychological stress and recurrences of HSV, whether it is the high levels of stress, anxiety and depression leading to frequent recurrences or frequent recurrences leading to increased stress is not clear. This is an issue that will be considered in the longitudinal study.

6.21 Overall Summary and Discussion

It can be seen that there are significant associations between the psychosocial measures and both (a) infectious illness in general and (b) cold sores in particular. These gross differences between the groups are removed, however, when negative affect (i.e. trait anxiety) was taken into consideration as a co-factor. It has been well documented that those high in negative affect are likely to report poorer psychosocial well-being and health/illness perception (e.g. Pennebaker, 1982) and this is, at first sight, borne out by the first set of analyses which took negative affect into consideration. However, it continues to be the case that this issue is frequently not taken into consideration when researching the relationship between stress and illness.

A rather different picture emerged when the severity of the illness was investigated. When the cold sore group were divided into those who suffered frequent recurrences and those who suffered few recurrences the differences between the more severe sufferers of cold sores (i.e. having a greater number of recurrences of the illness) and the control group were significantly higher than both the control group and the lower recurrence group. These differences largely remained significant even when taking into consideration the possible confounding variables of negative affect and previous illness. Those who may be considered to be suffering a severe form of herpes with frequent recurrences of HSV are clearly higher on the range of measures of psychosocial stress, depression and similar outcomes. Stress-related deficits in cellular immunity could well be an important factor in severity of illness and frequency of recurrence. The important issue raised here is that it is not appropriate to lump all cold sore sufferers into one group. Clearly there is a difference between those having the odd outbreak of cold sores and those who are suffering frequently recurring outbreaks. Whilst severity in terms of the duration and painfulness of each episode was not an important factor, severity in terms of the frequency of recurrence was. This is possibly due to the fact that painfulness and duration can be reduced by palliative treatment whereas there is no treatment currently available to prevent the actual recurrence of the cold sore. It is in this frequent recurrence group that a

significant relationship between illness and psychosocial stress and depression is found, and this relationship continues to be important even when previous illness and negative affect is taken into consideration.

Another indication of the immunosuppressive hypothesis is the finding that those who had higher incidence of cold sores also had higher incidence of other infectious illness than both the control group and the lower incidence cold sore group. It could be argued that this may be a consequence of reporting bias, however, the group did not report higher levels of other illness, only colds and upper respiratory tract infections. The higher scores on psychosocial measures at baseline, however, were not a consequence of previous illness; the differences in scores remained significant when previous illness was partialled out of the analysis.

This indicates a general vulnerability, possibly related to the immunosuppressive effect of high levels of stress and depression amongst the high incidence cold sore group which resulted in both greater frequency of recurrence of cold sores and greater incidence of other infectious illness.

It can be concluded from this cross-sectional analysis that those suffering frequent recurrences of cold sores scored significantly higher on measures of enduring psychosocial distress. These measures included both objective stress (i.e. negative life events and frequency of hassles) as well as their perceived ability to cope with these stressors. These individuals reported more negative mood and depression and scored lower on dispositional optimism. Measures of social support were significantly different between the groups when co-varying previous illness, but did not continue to be significant when negative affect was partialled out. The coping strategies of 'distancing' and 'escape avoidance' continued to be important with both the cold sore groups using more of these coping strategies. It may be the case that cold sore sufferers use these strategies to deal with their illness. Outcome measures of both cognitive and emotional difficulties were higher in the frequent cold sore group.

This study attempted to address a number of the general and specific methodological issues that had been discussed in the introduction, and also to investigate the relationship between those suffering from facial HSV and enduring psychosocial variables. There appear to be significant differences in the psychological profile of participants suffering from frequent recurrences of HSV, with the frequency of recurrence of the illness being an important issue. It also indicated that these individuals were subject to frequent recurrences of other infectious illness which indicated a potential immunosuppressive effect of perceived stress and depressed mood in this group.

Most researchers in the field of stress and illness recognise that longitudinal designs have significant advantages over cross sectional studies. The main criticism of cross sectional designs is the fact that it is not possible to determine any direction in the relationship between the potential predictor variable and the outcome variable. Do high levels of stress or negative mood cause a recurrence of illness or does the recurrence of the illness lead to high levels of stress. The advantage of the diary methodology used in the next study is that it allows for measurement of stress and infection recurrences at different points in time. Many longitudinal studies can be criticised for selecting only two points in time for the measurement of variables. Limited observation periods such as this also increase the possibility of chance associations and fail to provide any real understanding of the processual nature of stress. The more specific cause-and-effect relationship between (a) psychosocial mood and the recurrence of cold sores and (b) depressed mood and the recurrence of cold sores will be addressed in the next part of the study.

This longitudinal study is reported in the next chapter

CHAPTER 7

7.1 Introduction to Prospective Study of HSV

The specific nature of the relationship between psychological distress and HSV recurrence cannot be ascertained from cross-sectional studies. It is not clear whether psychological distress is a consequence or a cause of the recurrence of HSV. The next part of the study considers, more specifically, the role of psychosocial factors as causal agents in the recurrence of an episode of herpes simplex. As mentioned earlier, *most* of the studies in this area have been cross-sectional in design. This review of the literature considers those studies of herpes simplex which were longitudinal in design.

7.2 Review of Prospective Studies

One of the earlier studies was carried out by Luborsky, Mintz, Brightman and Katcher (1976) who found that greater *general* unhappiness was associated with more frequent cold sores in a sample of student nurses, although mood ratings 4 days before each episode were not good predictors of recurrence. More intense and/or sustained distress may be necessary to change immune function significantly to the point where a recurrence of the virus occurs.

Goldmeier and Johnson (1982) conducted a 28 week longitudinal survey and found that patients with higher scores on the General Health Questionnaire (GHQ) had their first recurrence sooner than those with lower scores, however, 13 of the 29 participants without recurrences were lost at the follow up stage and it is possible that distressed participants without recurrences may have dropped out of the study. Also GHQ responses may be influenced by concurrent illness which was not considered.

Hoon (1986) followed 122 participants for 6 months using monthly evaluations of major and minor life events. He found no correlation between negative life events in the preceding year and the number of reported recurrences in that year (NB: this study was retrospective and did not consider

subjective appraisal) however there was a significant relationship when monthly life events were correlated with concurrently reported monthly recurrences. This essentially was a cross-sectional analysis. A sub sample of 82 participants in this study were required to rate perceived stress weekly for 26 weeks. The researchers found no significant increase in stress ratings in the 2 weeks preceding a recurrence although their *physical* health rating increased in severity during the week of recurrence. Whether this was cause or effect is difficult to ascertain.

7.3 The Consequences of having a Recurrence of Herpes Simplex

Longo and Clum (1989) argued that stress arising from the disease itself primes patients for subsequent attacks and that stress affects immunocompetence and this causes recurrence setting up a vicious cycle. It is important, therefore, in any longitudinal investigation that the psychological after-effects of the previous attack must be taken into consideration. This is particularly important for those who suffer frequent recurrences.

Kemeny and colleagues (Kemeny, Cohen, Zegans & Conant, 1989) measured: (a) major life events, (b) ongoing daily stress, (c) negative mood, (d) helper inducer (CD4+) and suppressor cytotoxic (CD8+) T cells, (e) general health behaviour (sleep, exercise, alcohol and fatigue), (f) presence of other infections and (g) HSV recurrence. 36 participants with recurrent *genital* herpes were followed for 6 months, filling out questionnaires and being interviewed monthly. 19 of the participants gave blood samples for the immune measures. In this study they found that those with high levels of anxiety, depression or hostility had significantly lower CD8+ cells, high levels of stressors also resulted in lower CD4+ cells (cross sectional). Decreased levels of CD8+ cells were found to both *precede* and *follow* recurrent episodes. Over the 6 month period only 'other infection' had a close to significant relationship with recurrence rate. They suggested that infection may trigger recurrence in some individuals while others may have recurrences that are psychologically triggered. They tested this by using participants who did not report a large number of infection symptoms and found that the

depressive mood score (but not the total stressor score) was significantly related to recurrence in these participants. The depressive mood/ HSV recurrence relationship was not dependent on changes in health behaviours. In this study, the results were based on the average monthly scores over the 6 month period.

Kemeny and colleagues suggest that chronic levels of depressive affect may result in decreased levels of CD8+ cells (or a related immune parameter) which may result in HSV recurrence. However, acute changes in depressive mood were not related in time with acute changes in CD8 levels or increased recurrence of HSV in the following month. It is possible that short term changes in mood states are not sufficient to create immune changes but more chronic depressive disorders or traits are necessary to trigger recurrences. Furthermore, the frequency with which measures are made may be a significant factor and weekly measures may be more suitable than monthly measures for understanding the temporal relationship.

Results from Rand, Hoon, Massey and Johnson (1990) did not suggest that stress preceded recurrence. This again was a study of genital herpes and stress ratings on the day of, and the day after recurrence onset, were found to be significantly higher than pre-recurrence and non-recurrence days. They did find that for the 'stress believers' subset' there was a trend towards higher levels of stress in the 6 days before recurrence. This was a within-subjects design comparing pre-recurrence days and post-recurrence days in participants who were suffering from repeated recurrences of genital herpes during the period of study. No control group were used in this study. Confirmation of recurrence was made in a sub-sample of participants. 20 (25% of the original sample).of those interviewed for inclusion in the study dropped out,

In one of the few truly prospective studies Dalkvist and colleagues (Dalkvist, Robins Wahlin, Bartsch & Forsbeck, 1995) investigated the effect of psychological states measured *daily*, together with traits and other factors purported to be involved in HSV recurrence. They found a significant reduction in emotional well being, measured by rated nervousness and

alertness, over the ten days preceding recurrence of genital herpes. Females showed more of a trend towards reporting negative mood, and males for reporting more sleep difficulties. The results for oral herpes differed from the results for genital herpes. The common cold was a significant precipitating factor in oral herpes but not in genital herpes. Mood was *not* related to recurrence in the oral herpes group although there was a significant relationship on the sluggish/alert sub-scale. The authors suggest that the influence of mood on recurrence might be masked by the effects of the common cold which tended to occur at the end of the pre-recurrence period. Both exposure to sunlight and menstrual cycle had no effect on recurrence rate. Rates of recurrence (i.e. frequency of HSV) were not considered in this study. Mood was measured daily in this study for 3 months and participants were also asked to keep diary notes. The authors pointed out that there were a "large number of blanks in the diary data and some participants did not provide any notes at all" (page 129). This level of commitment for the daily rating scales might also be quite difficult to maintain.

Findings from prospective studies appear inconsistent with mixed results - a number of possible reasons for these different findings and problems with previous research have been discussed earlier. There are considerable variations in design between the studies and this clearly makes interpretation of the literature difficult. The issue of what constitutes psychological stress varies between studies. Many of the studies measure stressors and do not take into consideration subjective appraisal of stress. Measures of mood have been somewhat more prominent as precursors to outbreaks but it could be that these are measuring emotional distress. The distinction between more stable, dispositional traits such as depression and more transient (or acute) mood states is something that has been touched upon before. Most of the studies which have not found a relationship between mood and recurrence have been those that measured more transient mood state. It could be the case that emotional distress is not always measured by small changes in scores measured by certain bi polar mood adjectives such as happiness, concentration, and alertness.

It continues to be the case that studies of oral herpes are very thin on the ground. The majority of studies are of genital herpes that use participants attending clinics for treatment as the basis of the study sample. There is clearly a need for more research into oral herpes, particularly as there has been an indication that the relationship between psychological stress and HSV might be somewhat different compared to genital herpes.

Many of the earlier methodological considerations also apply to the prospective studies; research into the longitudinal relationship between psychological stress and/or depression and the development of HSV needs to take into consideration the following methodological issues:

1. Need for a control group
2. Need to measure objective and subjective stress
3. There are very few studies which address variability and extent of recurrence
4. Frequency of recurrence of HSV (both before and after the measures are taken) should be considered
5. Many of the studies use patients attending clinics or seeking help for psychological difficulties associated with genital HSV. This could result in a biased sample of participants with specific psychological problems.
6. Another methodological issue highlighted in studies of psychological factors and immune function /disease outcome is the wide range of social and behavioural factors such as substance use (i.e. drugs, alcohol, caffeine and smoking), diet, social class, occupation and age that can confound this relationship; Many studies have not controlled for the influence of these health behaviours.
7. The problem of negative affect and symptom perception needs to be controlled and concurrent illness as well as previous illness as potential confounding variables needs to be considered

7.4 Method

This longitudinal study followed on from the cross sectional study reported in the previous chapter. The recruitment of participants for inclusion in the study was described in study one and the demographic characteristics as well as the medical history and health behaviours were all described in the previous chapter.

After completing the baseline measures (described earlier) participants were given diaries which were required to be completed at the end of each week for 16 weeks. Diaries were to be returned each week after completion.

7.5 Weekly Diary (see Appendix A2.16)

The diary measured whether the respondent had developed any illness that week and if so what type; if an illness had occurred they were required to report on its severity, impact, any medication taken, the length of illness and the symptoms. The diary required participants to report whether they had developed a recurrence of herpes that week. Again, if they had, they were required to report on its severity, the length of the recurrence, its' impact, any medication used and the symptoms experienced. Measures were also taken of:

1. Health behaviours that week (sleep & alcohol consumption)
2. General health that week
3. Perceived Stress that week
4. Positive and negative mood that week
5. Major or minor distressing events and their impact, good or bad
6. The extent to which they felt they had coped with events that week
7. Symptom checklist

If the participant experienced a cold sore they were required to complete a further section of the diary in which they provided further details including (a) the date of onset, (b) the date it went away, (c) the severity and the painfulness of the outbreak, (d) medication used and (e) a symptom checklist.

7.6 Procedure

16 diary proformas were given to the participants on completion of the booklet containing the baseline questionnaires. Each diary was marked with the week (i.e. from 1-16) and an identifying participant number.

They were asked to complete the diaries on, or as near as possible to, the same day and time each week and to hand them back either to the experimenter or into the school office the following week. If there were holiday weeks or they were away, they were requested to complete the forms as usual and then hand them in when they returned to college.

Participants were asked to contact the experimenter as soon as possible if and when they did have a recurrence of herpes. Two contact numbers and an email address were given on the diaries. Herpes recurrences were verified in approximately 60% of cases. Those recurrences which occurred during holidays, weekends or when they were unable to come in to college were not verified. The controls were given the same diaries except that their dairy proforma did not ask about recurrences of HSV, only about recurrences of other illnesses.

The diaries ran from February/March to May/June for the HSV participants and from March/April to June/July for the healthy control participants. Participants were assured of the confidentiality of the information they provided and questionnaires were anonymously coded in order to ensure this.

7.7 Aims and Schedule of Analysis

1. To investigate the relationship between stress and stable psychological characteristics (measured at the beginning of the study) and subsequent recurrence of HSV.
2. To compare the HSV sufferers with the control group on the weekly diary measures during the period of assessment (i.e. weekly stress,

mood, negative events & hassles and frequency of other infectious illness). These measures were summed over the diary period

3. To compare the HSV sufferers who had at least one outbreak of cold sore during the diary period with those who did not have an outbreak of cold sore during this period on total stress and mood scores over the diary period
4. For those having recurrences of HSV during the diary period the severity of their outbreak was considered: (a) were baseline psychosocial measures higher for those having more severe outbreaks of cold sores than those having less severe outbreaks? (b) were those having more severe outbreaks of cold sore higher on the weekly measures of stress and mood summed over the diary period than those having less severe outbreaks?
5. To compare the three groups (i.e. controls vs. low recurrence HSV group vs. high recurrence HSV group) on frequency of recurrence of other infectious illness during the diary period, controlling for both previous illness and negative affect
6. To investigate the relationship between stress and stable psychological characteristics at baseline and the development of other infectious disease during the diary period in the HSV group (i.e. were those having frequent recurrences of other infectious illnesses higher on baseline psychosocial measures than those having few recurrences?)
7. To investigate the possible confounding effects of current and previous illness and negative affect in the relationship between psychological measures and subsequent illness
8. The analysis described in point 6 above was repeated for the control group
9. Finally, and importantly, whether stress and negative mood directly preceded a cold sore episode was investigated. The aim in this analysis was to investigate the temporal (i.e. week by week) relationship between the following variables and the subsequent recurrence of the HSV:
    a) Weekly perceived stress and cold sore outbreak
    b) Weekly mood state and cold sore outbreak

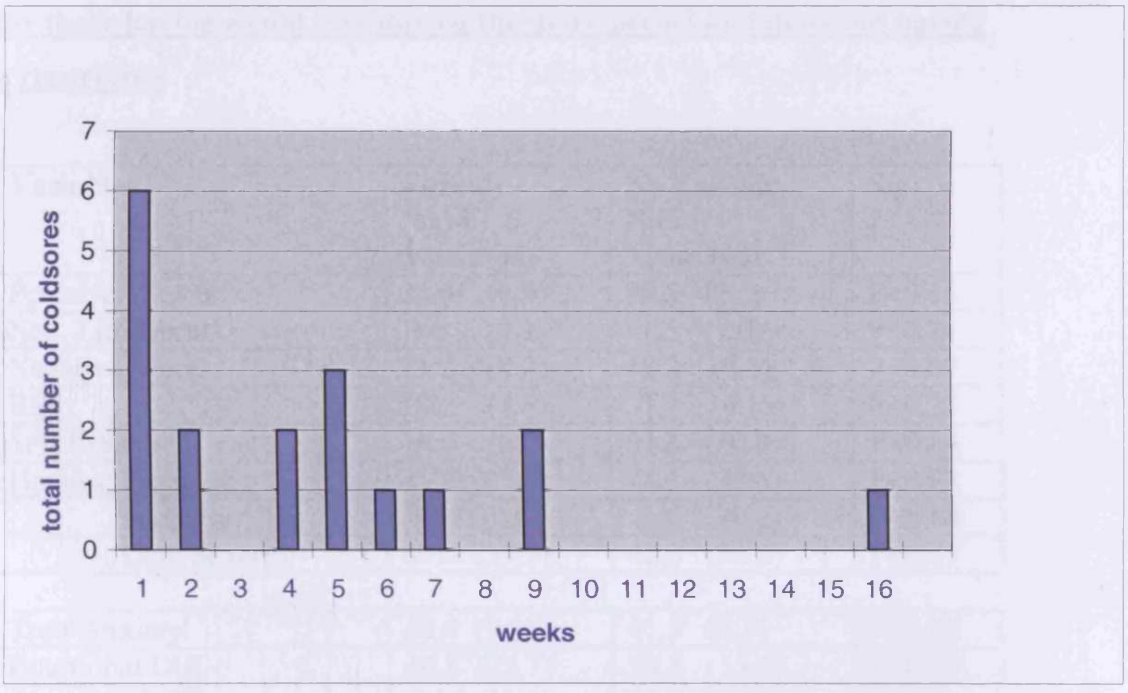
c) Weekly negative events and cold sore outbreak

d) This last analysis was repeated to investigate whether stress, negative mood etc. preceded the development of other infectious illnesses (i.e. colds & flu)

7.8 Results

The first section describes the frequency of recurrence of cold sores during the diary period. The number of participants suffering from an episode of cold sore recurrence each week is shown in the bar chart below.

Figure 3: the total weekly recurrence of HSV



There were 14 participants in the cold sore group who had suffered at least one episode of HSV recurrence, and there were six participants who had no episode during the diary period. From the above bar chart, it can be seen that over 85% of cold sore episodes occurred within the first seven weeks of the diary period.

Aim 1: to investigate the relationship between baseline measures of stress and psychological characteristics (measured at the beginning of the study) and the subsequent recurrence of cold sores.

This analysis focused on the herpes group only, comparing those who had a recurrence of herpes over the diary period with those who did not have a recurrence.

Firstly, differences between these groups on the standard psychosocial measures (taken at time one) were calculated using ANOVA and these are presented in the table below.

Table 35: Mean Scores (sd) on psychosocial measures taken at baseline for those having a cold sore during the diary period and those not having a recurrence

Variables	Episode N=14 Mean (sd)	No Episode N=6 Mean (sd)	Sig.
Perceived Stress	25.6 (6.9)	20.5 (7.2)	P<0.18
Neg. Life Events	2.6 (2.1)	1.5 (1.0)	P<0.24
Negative Mood	21.2 (9.3)	12.8 (8.5)	P<0.09
BDI	10.7 (4.7)	7.7 (4.1)	P<0.23
Self Esteem	44.0 (6.7)	55.3 (10.8)	**P<0.04**
Hassles: Frequency	31.2 (22.4)	28.3 (32.6)	P<0.83
Intensity	1.9 (0.6)	1.3 (0.2)	**P<0.04**
Cum Severity	64.0 (59.9)	42.0 (54.5)	P<0.47
Trait Anxiety	48.4 (9.3)	41.5 (8.1)	P<0.15
Emotional Diff.	46.2 (23.7)	33.5 (15.5)	P<0.26
Cognitive Diff.	34.4 (19.8)	26.2 (11.8)	P<0.37
Fatigue	32.0 (19.4)	24.3 (8.5)	P<0.37
Somatic Symptoms	40.2 (20.1)	33.2 (15.3)	P<0.48
Coping Strategies.			
Escape Avoidance	18.0 (5.8)	12.8 (2.8)	P<0.06
Seek Social Support	14.5 (3.8)	11.2 (3.5)	P<0.06

7.9 Summary

It can be seen from this data that whilst most of the differences between those having a cold sore and those not having a cold sore during the diary period did not reach significance, there was a consistent trend in the expected direction. Those participants having a cold sore were higher on measures of perceived and objective stress, negative mood, depression, hassles, trait anxiety, emotional and cognitive difficulty, fatigue and somatic symptoms. Clearly, the small number of participants in this analysis was problematic and if there had been a greater number this difference may have been achieved significance. The differences between the groups did reach significance for self esteem and intensity of daily hassles, These findings support the hypothesis that those participants higher on sustained psychosocial vulnerability factors are more likely to suffer recurrence of HSV-1 infections than those participants lower on these factors. Whilst the scores were consistently higher for the cold sore outbreak group the differences for all the variables did not always quite reach statistical significance. This is partly due to the relatively small numbers reflecting the difficulty of obtaining large samples of participants suffering from oral herpes (with frequent recurrences) in the community and recruiting them to prospective studies. This is probably the reason why the majority of research in this area has focused on genital herpes and recruits participants from those attending clinics for treatment.

7.10 Analysis of Weekly Diary Measures

Aim 2: Comparison of herpes group and control group on weekly scores: stress, mood, negative events, hassles and recurrence of other infectious illness

Weekly measures of stress, mood, general health, negative events and hassles were measured weekly. Stress, mood and health were scored on 5 point, likert scales where: 1 = very high stress/negative mood and 5 = very low stress/positive mood. The number of negative life events and hassles were counted., For the next analysis scores on these measures were summed over

the diary period and differences between the cold sore group and the control group were calculated. Firstly, scores were totalled for the **complete** period of diary keeping. The next table shows the summated scores for the cold sore participants compared with the healthy control group.

Table 36: Mean (sd) weekly diary scores (for the whole period) comparing the health control group with the cold sore group

Variable	Cold sore Mean (sd)	Controls Mean (sd)	Sig.
Total weekly stress (1=High 5=low)	36.2 (15.4)	52.3 (7.1)	P<0.0003
Total weekly mood (1=High 5=low)	39.9 (15.8)	55.4 (7.5)	P<0.0005
Frequency of other illness (weekly recurrence)	3.6 (2.1)	1.2 (1.2)	P<0.0004
Negative life events (weekly)	5.9 (4.1)	0.9 (1.5)	P<0.0000
Weekly hassles	4.9 (4.6)	3.6 (3.1)	non sig

It can be seen that the cold sore group were significantly higher in stress and negative mood over the diary period than the control group. They also experienced more negative events and suffered more illness than the control group during this period.

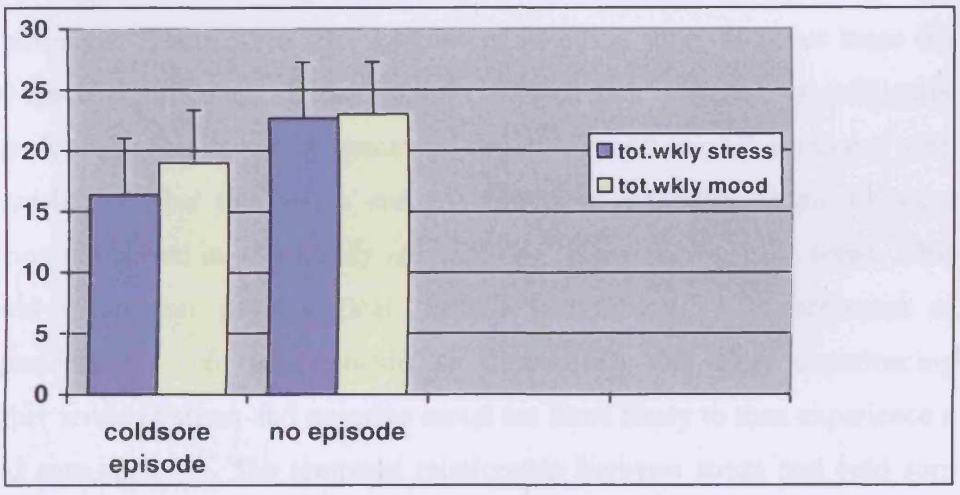
7.11 Weekly Stress and Mood Scores for the Cold Sore Group only, Comparing those who had a Recurrence with Those who did not have a Recurrence during the Diary period

Aim 3: Were those having a cold sore during the diary period higher on total weekly stress and negative mood than those not having a cold sore during the period?

Because 85% of cold sore recurrences occurred within the first 7 weeks of the diary period this is when it might be expected that differences in stress and mood would be apparent. Weekly stress and Mood scores over the first seven weeks were calculated for those who had an episode of cold sore compared with those who did not have an episode. ANOVAs were calculated to test the difference in scores for cold sore episode and no episode conditions (i.e.

experimental group only). (N.B. a lower score = higher stress levels and less negative mood) The following bar chart shows the differences in stress and mood scores during the first seven weeks of the diary period for those having a cold sore infection and those who did not have a cold sore infection during this period.

Figure 4: Mean stress and mood scores for cold sore and no cold sore Groups (low score=greater stress and more negative mood)



Those having a cold sore during the diary period had a mean stress score of 16.42 (*sd*=5.43) compared with a mean stress score for the no episode group of 22.67 (*sd*=4.63). A low score means higher stress and the difference between the group was significant ($p<0.02$). The differences between the groups on total weekly mood was not significant but was in the anticipated direction; mean score for cold sore episode group was 19.00 (*sd*= 5.77) and for the no episode group (23.0 (*sd*=4.29) $p<0.15$. Again, a lower score means higher negative mood.

7.12 Summary

It can be seen from the above set of analyses that the cold sore group as a whole were significantly higher than the controls on measures of stress and negative mood, weekly measures of negative events as well as the frequency

of other infections. This finding is similar to Hoon's (1986) finding of correlations between monthly recurrence of cold sores and negative life events. Although these events are concurrent with recurrence of cold sore, it does not necessarily mean that stress and negative mood directly preceded the outbreak of cold sores. The next analyses focused on the cold sore group only, to investigate whether there were within-group differences between those having an outbreak of cold sore and those not having an outbreak of cold sore during the period of assessment. It was found that those experiencing a recurrence were significantly higher in reported levels of psychological stress during the period in which they were experiencing these recurrences. There were also differences in mood state, however these did not reach significance. These findings suggest that sufferers of cold sores experience higher levels of stress and negative mood overall compared with controls, but that this stress and psychological difficulty seems to occur during the period in which they are suffering recurrences of cold sores. This could mean that psychological distress increases as a consequence of experiencing a cold sore episode, or alternatively that those experiencing higher levels of stress and negative mood are more likely to then experience a cold sore episode. The temporal relationship between stress and cold sore episodes is discussed further in Section 6.24.

7.13 Severity and Length of Cold Sore Recurrence

Aims 4a and 4b. Differences between those having more severe cold sore and those having less severe cold sore episodes during the diary period

Again, within the cold sore group, those suffering a recurrence of cold sore were analysed in terms of the severity of their cold sore recurrences.

a) baseline measures in relation to severity

Firstly the relationship between psychosocial measures and subsequent severity of cold sore episode was analysed. For those who suffered an outbreak of herpes during the diary period, measures of severity and length

of outbreak were taken into consideration. The relationship between psychosocial measures taken at baseline and subsequent length and severity of outbreak were analysed. Weekly severity scores were divided by the number of outbreaks to obtain an average perceived severity score per episode. The group was split into those who perceived their outbreaks of herpes to be mild and those who perceived their outbreaks, on average to be either moderate or very severe. Anovas were calculated to measure differences between those having less severe cold sores and those having more severe cold sores on a range of baseline psychosocial measures are shown in the following table.

Table 37: Mean (sd) scores on baseline psychosocial variables and subsequent severity of cold sores

Psychosocial Measure	**Less severe outbreak. (n=4) Mean (sd)**	**More severe outbreak. (n=6) Mean (sd)**	**Significance**
Perceived Stress	22.7 (7.4)	30.0 (3.2)	0.10 n.s.
Negative Life Events	1.5 (1.5)	4.2 (1.7)	0.02
Total Life Events	2.5 (1.6)	6.3 (1.5)	0.006
Daily Hassles: Cumulative Severity Frequency	45.5 (48.7) 22.7 (19.1)	91.8 (71.5) 44.8 (22.2)	0.25 n.s 0.12 n.s.
Beck Depression Inventory	8.3 (3.3)	14.0 (4.9)	0.05

Not all of the baseline measures significantly predicted the severity of subsequent cold sores; the personality measures, coping and social support were not related to severity. There were however significant relationships between (a) negative life events and severity of outbreaks and (b) depression and subsequent severity of outbreaks. The difference between the groups on perceived stress and the severity and frequency of daily hassles, whilst not quite significant did indicate a trend in this direction. It would appear that stress and depression at baseline may be related to subsequent severity of cold sore outbreaks. The numbers in this analysis were small.

The next set of analyses considered severity of outbreak and scores on negative mood and stress during the diary period.

b) severity of episode, total stress scores and mood scores over the diary period

The following table shows the total weekly stress and mood scores for those having less severe cold sore episodes and those having more severe cold sore episodes. These were the weekly stress and mood scores summated over the diary period where higher scores meant lower stress/mood.

Table 38: Mean (sd) weekly stress and mood scores for those having less severe cold sore episodes and those having more severe cold sore episodes

Measure (low score=high stress/mood)	**Low Severity Mean (sd)**	**High Severity Mean (sd)**	**Significance**
Total Weekly Stress	46.3 (8.7)	38.5 (21.0)	0.51 n.s.
Total Weekly Mood	42.5 (12.7)	34.2 (18.9)	0.47 n.s.

The total stress and mood scores during the diary period, whilst being somewhat higher in the high severity group, did not reach statistical significance. This was similarly the case for length of outbreaks.

7.14 Summary

There is some evidence that the baseline measures of objective stress and depression were associated with the later severity of the cold sore outbreak, however the overall scores for stress and negative mood during the diary period were not significantly higher. Whilst there did appear to be a trend in the expected direction the possibility of these differences being due to the possible confounding factors of negative affect and/or previous illness also needs to be considered. These findings suggest that there is potentially

important relationships between baseline measures and subsequent development of cold sores as well as severity of the cold sores suffered, however, and this is something that could be investigated further with greater numbers of sufferers.

The next set of analyses considers the issue of other infectious illness as well as the issue of confounding variables..

Aim 5: Difference between healthy controls, & cold sore groups (i.e. low and high cold sore recurrence) on recurrence of other infectious illness

The cold sore group were divided according to whether they suffered frequent recurrences of cold sores or not and the differences between these three groups were analysed. The next table shows the scores for these three groups on the frequency of subsequent illness. Frequency of subsequent illness refers to the number of infectious illnesses reported over the diary period. Also in this analysis the potential confounding effect of negative affect and previous illness are taken into consideration.

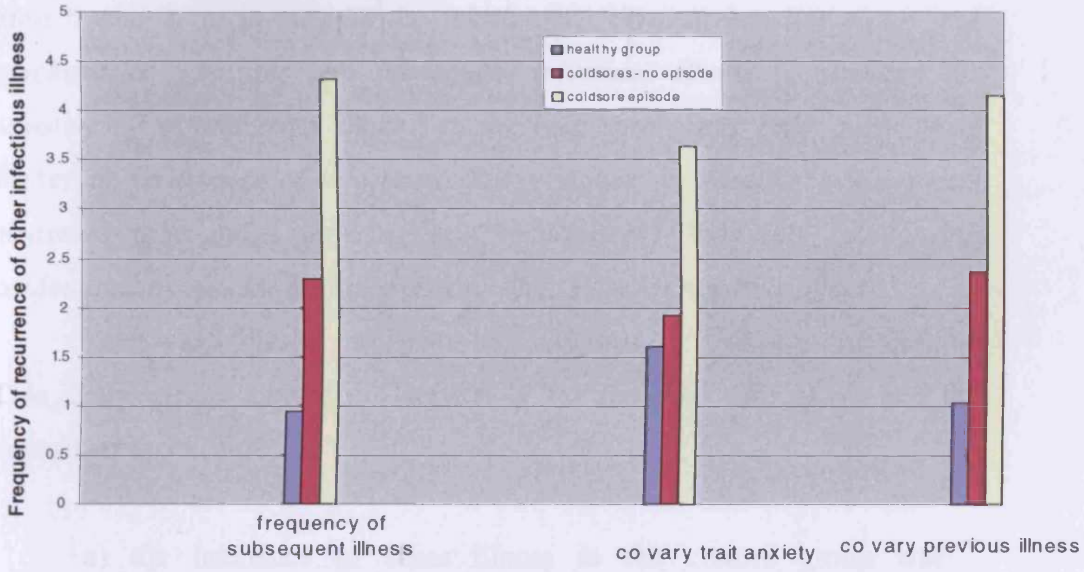
Table 39: Mean (sd) frequency of recurrence of other infectious illness in the low incidence cold sore group, the high incidence cold sore group and the healthy control group during the diary period, co-varying negative affect (n.a.) and previous illness

	3. Non Cold sore Mean (sd)	2. Cold sore – Low Incidence Mean (sd)	1. Cold sore –Higher Incidence Mean (sd)	Post Hoc Tukey Test
Frequency of subsequent illness. ***	0.94 (1.0)	2.29	4.31	1 & 3 ** 1 & 2 *
Co-vary n.a. **	1.61	1.92	3.63	
Co-vary Prev. Illness ***	1.03	2.37	4.15	

***** = P<0.001, **=P<0.01 *=P<0.05**

These findings are also depicted in the bar chart below which clearly shows the important differences between the groups on the recurrence of other infectious illness during the diary period.

Figure 5: Mean frequency of the recurrence of infectious illness during the diary period for low incidence cold sore group, the high incidence cold sore group and the control group.



7.15 Summary

These results clearly indicate a significant relationship between the frequency of cold sore recurrence and the subsequent recurrence of other infectious illness during the diary study. This relationship remained significant when both trait anxiety and other previous illnesses were co-varied. Those who were categorised as high 'incidence cold sores', based upon the number of outbreaks they reported experiencing during the past 12 months, were significantly more likely to suffer more frequent recurrences of infectious illness, largely colds and influenza. This was not a consequence of the higher incidence cold sore group having a lot of previous infectious illnesses. The problems associated with self-reported health and illness and negative affect was discussed earlier and this analysis took negative affect into consideration

in this analysis. Furthermore the role of previous illness was also considered here and the relationship between chronicity of cold sores (i.e. frequency of outbreaks) was associated with increased levels of other infectious illness during the diary period.

7.16 The Relationship between Psychosocial Measures and Subsequent Development of other Illness

Aims 6 and 7: to investigate the relationship between baseline stress and psychosocial measures and subsequent infectious illness (controlling for negative affect and other illness) in the cold sore group only: were those higher in recurrence of infectious illness higher on baseline psychosocial measures than those suffering few recurrences? Was this relationship confounded by current illness, previous illness and/or negative affect?

This analysis was carried out separately for the cold sore group and the control group because:

a) the incidence of other illness in the control group was significantly lower. Only 5 controls had more than two illnesses during the diary period
b) To see whether the relationship between psychosocial measures and subsequent illness was related to previous recurrence of cold sores or not
c) To see whether the relationships were the same for both the control group and those suffering from cold sores

Those of the cold sore group who developed three or less illnesses during the diary period were compared with those who developed four or more other illness. This was based on a median split where the mean number of infectious illnesses was 3.6 median was 4. This analysis is carried out with the cold sore only group and the incidence of previous cold sore episodes, incidence of other previous illness and negative affect were taken into consideration. The next table shows the differences between these groups

(low incidence and high incidence of infectious illness groups) on baseline psychosocial measures i.e. do those who subsequently develop more infectious illness during the diary period have higher scores on measures of stress and psychosocial measures taken at baseline.

Table 40: Mean (sd) scores on baseline psychosocial measures for those low and high in frequency of infectious illness during the diary period (controlling for previous illness, previous coldsore recurrence and negative affect (NA))

Psychosocial Measure	Developed Less Than 4 Illnesses N=9 Mean (sd)	Developed 4 Or More Illnesses N=11 Mean (sd)	Significance
Perceived Stress	20.0 (7.9)	29.9 (4.5)	P<0.002
Co-vary previous illness	20.4 (2.9)	29.3 (1.7)	P<0.002
Co-vary previous cold sores	20.3 (2.5)	29.1 (2.1)	P<0.01
Co-vary NA	22.3 (2.6)	27.6 (1.9)	P<0.05
Total Life Events	3.1 (2.5)	5.0 (1.9)	P<0.06
Co-vary previous illness	3.2 (0.9)	4.9 (1.2)	P<0.07
Co-vary Previous Cold sores	3.1 (0.8)	5.2 (1.3)	P<0.06
Co-vary NA	2.9 (0.9)	5.1 (1.3)	P<0.07
B.D.I.	6.7 (5.2)	11.6 (5.7)	P<0.009
Co-vary Previous Illness	6.6 (1.0)	11.7 (1.6)	P<0.009
Co-vary Previous Cold sores	6.9 (1.1)	11.5 (1.5)	P<0.02
Co-vary NA	7.5 (1.2)	11.1 (1.2)	P<0.05
Hassles:			
Frequency	18.6 (11.2)	39.1 (5.2)	n.s.
Cumulative Severity.	39.0 (19.5)	65.0 (22.4)	n.s.
Negative Mood	12.5 (7.5)	22.6 (8.3)	P<0.008
Co-vary Previous Illness	12.6 (1.3)	22.6 (2.2)	P<0.01
Co-vary Previous Cold sores	12.5 (1.2)	22.7 (1.9)	P<0.01
Co-vary NA	16.5 (1.5)	19.5 (1.5)	n.s.
Emotional Difficulty	30.4 (9.9)	51.5 (20.8)	P<0.01
Co-vary Previous illness	30.4 (4.8)	51.56 (5.2)	P<0.01
Co-vary Previous			

cold sores	31.4 (4.7)	51.0 (5.1)	P<0.03
Co-vary NA	38.9 (4.3)	44.62 (5.5)	n.s.
Cognitive Difficulty	20.9 (15.2)	39.5 (11.8)	P<0.005
Co-vary Previous Illness	21.2 (2.8)	39.3 (3.8)	P<0.008
Co-vary Previous Cold sores	22.1 (2.9)	38.6 (3.6)	P<0.02
Co-vary Trait Anxiety	24.7 (3.0)	36.4 (3.4)	P<0.09
Somatic Symptoms	29.6 (13.0)	45.8 (17.6)	P<0.03
Co-vary Previous Illness	29.9 (2.1)	45.5 (4.4)	P<0.04
Co-vary Previous Cold sores	31.2 (2.2)	42.6 (4.5)	n.s.
Co-vary NA	34.7 (2.5)	41.6 (5.3)	n.s.
Total ISEL	117.9 ((16.8)	116.23 (15.4)	Ns
Coping Strategies: Problems Solving	11.8 (3.1)	15.8 (3.9)	P<0.03
Covary Prev. ill	11.9 (1.0)	15.25 (1.4)	P<0.04
Covary Prev cold sores	11.8 (0.8)	15.4 (1.2)	P<0.06 ns
Covary NA	11.2 (0.9)	15.9 (1.3)	P<0.02
Conf. Coping	10.8 (2.9)	14.4 (2.8)	P<0.02
Covary prev. ill	10.9 (0.8)	14.2 (0.7)	P<0.02
Covary prev cldsre	11.1 (0.8)	14.4 (0.8)	P<0.05
Covary NA	10.6 (1.0)	14.5 (0.9)	P<0.04
Positive Readjust	12.3 (4.1)	16.7 (3.5)	P<0.03
Covary prev. ill	12.6 (1.5)	16.5 (1.2)	P<0.02
Covary prev cldsre	12.8 (1.5)	16.6 (1.1)	P<0.08 ns
Covary NA	12.7 (1.3)	16.4 (1.2)	n.s.
Self conf.	14.3 (2.9)	17.7 (4.5)	P<0.06 ns
Covary prev illness	14.5 (0.8)	17.6 (1.4)	P<0.08 ns

7.17 Summary

Within the cold sore group, there was a significant association between most of the psychosocial measures taken at baseline and the subsequent development of other infectious illness. This effect largely remained significant when controlling for both previous illness and incidence of previous cold sores and trait anxiety. Perceived stress was significantly higher for those developing more illnesses, as were total life events and depression scores. The relationship between daily hassles and subsequent development of illness, whilst not reaching significance was in the expected direction.

Negative mood, emotional difficulty, cognitive difficulty and somatic symptoms were significantly higher in the group who subsequently developed more illness. Whilst this difference remained when previous illness and previous incidence of cold sores were controlled, it no longer reached significance when negative affect was co-varied. There were no significant differences in self esteem, optimism and social support, however the coping strategies of problem solving and confrontive coping were used significantly more by those developing more illnesses.

High levels of perceived stress and depression were the most significant psychosocial variables in relation to subsequent illness. These measures are important measures of psychological distress and might be considered important and enduring psychological vulnerability factors in relation to ill health. It can be concluded from this analyses that respondents who suffer from recurrences of cold sores are more likely to develop other infectious illness than those who do not suffer from cold sore recurrences; within the cold sore group high baseline scores on psychological stress and depression are associated with the subsequent development of high levels of other infectious illness. This was not a consequence of negative affect influencing symptom perception and was not associated with current or previous illness.

Aim 8 : To consider the relationship between baseline psychosocial measures and subsequent development of infectious illness in the healthy controls

In order to assess whether the same processes occurred within the healthy controls, the same analysis was conducted but this time using only the healthy control group. The relationships between (a) previous illness and scores on the psychosocial measures and (b), the relationship between psychosocial measures and subsequent development of illness were investigated.

There was a significant relationship between more previous illness and perceived stress, negative life events, hassles, depression, emotional and cognitive difficulty and self esteem in the control group; these relationships had not been significant when looking at the cold sore group. The differences

between 'low previous illness' and 'higher previous illness' on baseline psychosocial measures for the control group were mostly significant, whilst for the cold sore group this was not the case. However, the incidence of infectious illness for the control group (even for the higher illness participants) was still substantially lower than even the low illness participants in the cold sore group. Overall, the cold sore group scored significantly higher than the control group on these psychosocial measures, and their scores appear to be less affected by previous illness than for the control group.
(See tables of ANOVAs and ANCOVAs in Appendix A3.12 and A3.13).

7.18 Subsequent Development of Illness over the Diary period in the Control Group

The control group were divided into those (a) who developed two or more illnesses during the period (i.e. more illness) and (b) those who developed one or no illness (i.e. less illness); the relationship between psychosocial measures at baseline and the development of either 'less' or 'more' illness was considered. An important point here is that the control group developed significantly fewer other illness, and whilst it was possible to make a sensible split for the cold sore group into low and high illness groups, in the control group the number who suffered 2 or more illnesses was only five participants. The majority of healthy participants suffered no illnesses or only one cold during the period of assessment (see Appendix 3 for tables of ANOVAs and ANCOVAs).

There was a significant relationship between baseline scores on (a) perceived stress, (b) depression and negative mood, (c) self esteem and low optimism, (d) emotional difficulties, and (e) greater use of certain coping strategies and the subsequent development of more illness in the control group. Although the overall rates of illness were substantially lower (even for those in the higher illness group) than the scores for the cold sore group, there was a similar trend in both groups for higher baseline psychosocial scores to be related to subsequent development of illness.

In the cold sore group this was a very robust relationship, which remained significant even when controlling for trait anxiety and previous illness; in the control group the relationship was no longer significant after trait anxiety was controlled. Generally in the control group higher trait anxiety may account for the relationship between self-reported psychological stress and higher levels of illness. This was not the case in the chronic illness group (i.e. those suffering frequent recurrence of cold sores). This is similar to the findings in study one which demonstrated that frequency of illness is an important factor in relation to psychosocial stressors. It would again appear that those suffering more frequent recurrences of infectious illness are significantly higher on the measures of psychological stress and depressed mood and that in this group the differences are not a consequence of negative affect (as measured by trait anxiety) or previous illness. Furthermore, these psychosocial measures were taken prior to the development of infectious illness and therefore preceded them. This supports the finding in the cross-sectional cold sore study that those with frequent recurrences are the ones in which there are significant associations between psychosocial measures and recurrence. The trends were similar in both groups and overall the healthy group were more healthy, developing less illness and scoring lower on the psychosocial measures. The relationship between frequency of illness other than cold sores and psychological stress in the healthy group appeared to be a consequence of higher negative affect influencing responses on these self-reported measures of stress and illness.

7.19 Conclusion

It would appear from this analysis that there are important relationships between the psychosocial measures at baseline and the subsequent development of both cold sores and other illness. In the cold sore group it did not appear to be previous illness resulting in the subsequent high scores on stress and depression, but rather the high scores on these measures relating to the *subsequent development* of other infectious illness. This relationship was robust and continued to be significant when trait anxiety and previous illness were co-varied; the critical factor was the frequency of illness with high

frequency of illness being a major issue i.e. there was a significant difference between low frequency of recurrence of illness and high frequency of recurrence of illness on baseline psychosocial measures and this differences was largely maintained when negative affect and previous illness was co-varied.

In the control group, previous illness was related to subsequent psychosocial measures, although in the control group only 4 participants actually suffered from 2 or more illnesses. There was a significant association, in the control group, between baseline psychosocial measures and reported illness during the diary period, however, the association did not remain significant when negative affect was co-varied. In other words negative affect could account for illness reporting and high scores on the psychosocial variables in the healthy control group. Furthermore, it must be remembered that overall scores were substantially lower in the control group.

7.20 Temporal Relationships between Weekly Stress, Mood and Recurrence of Cold sores during the Diary period

Aim 9: to investigate whether stress, negative mood, negative events directly precede the outbreak of herpes in the diary study

The first set of analyses considered the role of changes in stress, negative mood, negative events and the recurrence of cold sores.

7.21 Stress and HSV Recurrence

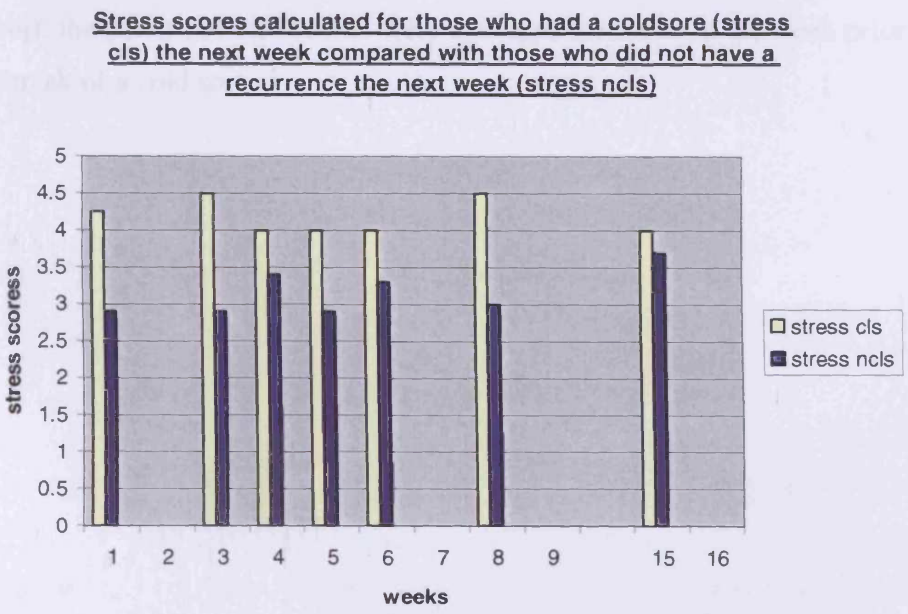
There was a clear pattern in each of the participant's weekly scores for an increase in stress in the week prior to the cold sore recurrence and then to decrease afterwards. This indicated that stress was a factor in the development of cold sores and not simply a consequence of it, this was investigated in the next series of analyses.

7.22 Group Patterns

A graph was plotted depicting the stress scores for those who had an episode in the subsequent week compared with those who did not (i.e. stress scores were calculated for the week prior to recurrence of the infection). The figure below shows the stress scores for those having a cold sore outbreak the week before that outbreak and the stress scores for the same week in those who did not subsequently develop a cold sore.

Figure 6: Mean stress scores for the week prior to a cold sore outbreak for those with and without cold sore recurrence in the subsequent week

The legend refers to 'stress cls' which is the stress score for those participants who developed a cold sore the following week and 'stress ncls' which refers to the stress scores for those participants who did not develop a cold sore the following week.



It can be seen that there were consistent differences between the stress scores in the week prior to an outbreak of HSV; the weekly stress scores in the

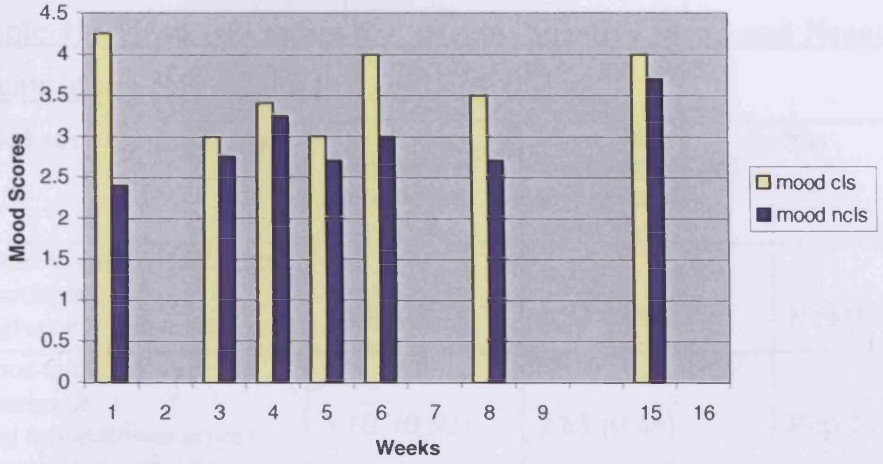
'subsequent recurrence' group were consistently higher than for the 'no subsequent recurrence' group. However, this did not take into consideration the possible confounding effects of having a cold sore in the previous week i.e. the possible after effects of having a cold sore. In the subsequent analysis the potential confounding effects of the after effects of a cold sore were controlled but firstly the relationship between mood and HSV recurrence was considered.

7.23 Mood and HSV Recurrence

The same analysis was carried out for mood scores **with the difference** in mood scores in the week prior to an outbreak of herpes calculated for those who subsequently developed a recurrence and those who did not. The following figure shows that the pattern was not as marked for mood as it was for perceived stress. It can be seen that for the outbreaks in weeks 2, 7 and 9, the mood scores were higher for those developing an infection; however this was not as marked for the outbreaks in weeks 3, 4, and 5. Whilst not as robust, the pattern of differences were the same for mood in the week prior to outbreak of a cold sore.

Figure 7: Mean mood scores the week prior to cold sore or no cold sore episode.

Mood scores were calculated for those who had a cold sore recurrence in the next week group (moodcls) compared with those who did not have a cold sore recurrence in the next week. (moodncls).



7.24 Analysis of diary measures

The relationship between weekly stress; weekly mood and weekly negative events and the subsequent recurrence of cold sores was investigated.

7.24.1 Stress

In order to analyse this relationship it was necessary to measure the stress scores the week prior to an outbreak of cold sore and to see whether there was a significantly higher stress score for those who developed a cold sore than those who did not. It was also necessary to exclude the stress score from the previous week for those who were having an outbreak that week, to avoid confounding pre-cold sore stress with post-cold sore stress. Stress scores for those with a cold sore the previous week were excluded from the total stress score.

The same analysis as above was carried out for the relationship between (a) weekly mood scores and cold sore recurrence and (b) weekly negative events and cold sore recurrence. Mean scores were compared for the week prior to an outbreak of cold sores with scores for the week prior to no outbreak (NB: low score = high negative mood). The following table shows the scores for stress, negative mood and negative events.

Table 41: Mean (sd) scores for Stress, Negative Mood and Negative events in pre cold sore/pre-no cold sore episode

Cold sore Group Only	Mean Value Week before No cold sore Mean (s.d.)	Mean Value Week before Cold sore outbreak Mean (s.d.)	Sig.
Stress and cold sore recurrence (high stress = low score)	2.84 (0.54)	1.83 (0.41)	P<0.001
Mood and cold sore recurrence (neg mood=lower score)	3.10 (0.52)	2.61 (0.49)	P<0.13 ns
No. of Negative events and cold sore recurrence.	0.57 (0.35)	1.27 (0.60)	P0.07 ns

There was a significant difference in the stress scores in the week prior to an outbreak of cold sore and the week prior to no outbreak of cold sore. This difference was highly significant and remained when controlling for the after-effects of previous illness.

There was no significant relationship between negative mood and recurrence of cold sore as measured in this diary study, this was similarly the case for weekly negative events. Although the differences were not significant for weekly mood and negative events the trend was in the anticipated direction.

It can be seen from these results that there is a significant relationship between high levels of stress and subsequent outbreak of cold sores in the following week. There is also an 'after-effect' of a cold sore episode, and the episode itself may cause stress and negative well-being. In this study,

however, if participants who were in the aftermath of a previous infection their stress scores were excluded from the analysis on that week.

This analysis was a between-subjects design, comparing the stress levels of those who had a subsequent outbreak and those who did not, within the cold sore group. The relationship was not significant for negative mood or negative events

Aim 10: investigate the relationship between stress, mood, negative events and infectious illness recurrence in the whole group (cold sore and controls combined).

The temporal relationship for the all participants (controls and cold sores) between weekly stress and recurrence of other infectious illness was analysed as well as in the temporal relationship between both negative mood and negative events and recurrence of other infectious illness during the diary period. Scores for these variables were compared the week prior to the development of colds or flu with scores the week prior to no incidence of illness. If the participants had experienced an illness in the week before the development of the illness, they were excluded from the analysis in order that the measures would not be contaminated by the possible 'after-effects' of illness. The following tables show the results of this analysis.

Table 42: Mean Scores for Stress, Negative Mood and Negative Events in the week prior to the development of an infectious illness compared with the week prior to no infectious illness

Whole Sample:	**Mean Value Week before no illness Mean (s.d.)**	**Mean Value Week before illness episode Mean (s.d.)**	**Signifi-cance**
Stress and infectious illness recurrences	2.86 (1.13)	2.35 (0.63)	P<0.03
Mood and infectious illness recurrence	3.09 (1.12)	2.74 (0.51)	P<0.10 ns
No. of Negative events and infectious illness recurrence.	0.43 (0.53)	0.09 (0.16)	P<0.20 ns

There was a significant difference in the stress scores in the week prior to developing an infectious illness compared with the week prior to no illness. This held when removing from the analysis those suffering from an illness in the week prior to the stress measures. The differences were not significant for mood or negative events, although the trend was in the anticipated direction.

7.25 Discussion

Overall, the results suggest that in considering the relationship between psychosocial factors and illness it is vitally important to consider the role of negative affectivity and previous illness. Whilst it may appear that there were very large differences between the cold sore group and the healthy controls, these basic differences in psychosocial measures could largely be explained in terms of previous illness and negative affect. It transpired, however, that the critical factor when considering the role of psychosocial factors was the *frequency* of illness recurrence. When the frequency of the illness was taken into consideration it was clear that the differences between scores on psychosocial measures for the groups was highly significant, even after controlling for the effect of previous illness and negative affect. The critical factor appears to be ongoing, frequent recurrence of illness not necessarily the severity or painfulness of those infections once they occur. The painfulness and duration of each episode can often be controlled by palliative treatment, however, the frequency of recurrence cannot be. Those having frequent recurrence of the illness scored significantly higher on (a) objective and perceived stress, (b) depression and negative mood, (c) pessimistic outlook, and (d) cognitive and emotional difficulties.

It was also clear that those having frequent recurrences were subject to more illness than the healthy control group and the low incidence group and that included previous infectious illness as well as subsequent illness. However, there were no significant differences between those having a lot of other previous illness and scores on psychosocial measures. Furthermore, previous illness and negative affect were controlled in the analysis and the high

incidence cold sore group continued to score higher on measures of psychological stress, depression, and other psychosocial measures. This suggests that it was not so much the 'after-effects' of previous illness causing high scores on psychosocial measures but rather the high scores on the psychosocial measures preceding the development of more frequent recurrence of HSV as well as recurrence of other infectious illnesses in the HSV group.

7.26 The Role of Previous Illness (no. of reported colds, flu and URTIs in past 12 months) and frequency of recurrence of infectious illness during the diary period

In order to consider in more detail whether previous illness (i.e. the number of reported colds, flu and upper respiratory tract infections in the past 12 months) resulted in higher scores on psychosocial measures, the cold sore group were divided into those who had suffered from more infectious illnesses in the past twelve months and those who had suffered fewer other infectious illness episodes in the past twelve months. There was no evidence of previous illness being related to psychosocial measures but, there were significant associations between psychosocial measures taken at baseline and the frequency or reported colds, flu and URTIs during the diary period in the cold sore group. When the group were divided into those who developed 4 or more infectious illnesses during the diary period and those who developed less than 4, it could be seen that high scores on psychosocial measures of negative life events, perceived stress, depression and cognitive difficulty were significantly associated with the subsequent development of more illness. This relationship remained significant even when previous illness and negative affect were co-varied. In HSV group, those higher in perceived and objective stress and depression were likely to have significantly more recurrences of infectious illness during the diary period which was not a consequence of previous illness or negative affect.

These findings suggest a general vulnerability, possibly related to the immunosuppressive effect of high levels of stress and depression amongst the

high incidence HSV group, which resulted in both greater frequency of recurrence of HSV as well as a greater incidence of other infectious illness. This was an important longitudinal finding where baseline measures of both stress and depression taken at time one were significantly associated with the subsequent recurrence of illness over the following 16 weeks. The issue of 'illness vulnerability' was raised by Hoon et al (1991) and whilst they did not find a relationship between stress and HSV recurrence suggested that stress effects illness vulnerability which in turn affects recurrence rates. The novel finding in this study was the focus on those suffering frequent recurrences of HSV. It could be the case that in those sufferers who only experience an occasional recurrence the role of psychosocial factors may be minimal, however, in those who suffer frequent recurrences, psychological stress appears to play a significant role.

7.27 Stress and Illness in the Healthy Control Group

In order to investigate whether the same processes occurred in a healthy population, the same analyses were carried out in the control group. In this group, however, there were relatively low levels of illness in general; illness levels even for the higher illness (but non-HSV) group were substantially lower than for the low illness HSV group. It did initially appear that for the control group, higher levels of previous illness was associated with higher scores on psychosocial measures, though this relationship was no longer significant when negative affect was co-varied. This was similar for reported recurrence of infectious illness during the diary period, with a significant difference between those higher in frequency of reporting illness and those lower in reported illness on baseline psychosocial measures; however, once again this was cancelled out when co-varying negative affect and previous illness. Whilst this finding may be more to do with the overall low levels of illness recurrence in the healthy control group, it would seem that in the healthy group as well as the low recurrence HSV group, psychological stress and depression did not relate to the later development of infectious illness.

This study, and others, provides evidence for the role of negative affectivity influencing self-reported psychosocial measures, and whilst this may account for the differences in illness occurrence in the control group and the low incidence HSV group, this does not appear to account for the differences found in the high frequency HSV group, and also those suffering high levels of other illness. The differences between the control group and the high incidence HSV group on a range of psychosocial measures remained significant when negative affect and previous illness were controlled. Within the HSV group there was a robust effect of psychosocial measures on subsequent illness, and again this remained significant even after controlling for negative affect and previous illness. Whilst negative affect and previous illness appear to account for some of the differences in measures of stress and depression between the healthy controls and the HSV group, its influence does not provide the full explanation for the differences found in the HSV group. There were large differences over and above the effect of both previous illness and negative affect.

7.28 Diary Measures

Analysis of the diary study provided evidence for higher levels of stress and negative mood amongst the HSV group during the diary period and considered more carefully the temporal relationship between stress and mood and both HSV recurrence and the recurrence of other infectious illness. Firstly the differences between those having an outbreak of cold sore in the diary period and those not having an outbreak during that period were considered and there was a trend for those subsequently developing a recurrence to have higher scores on baseline psychosocial measures of stress and depression; the differences provided an indication only because whilst there was a consistent trend for baseline psychosocial measures to be associated with the subsequent HSV recurrence the differences did not quite reach statistical significance. The trend was similar for all the baseline psychosocial measures. Because 4 of the participants who were suffering outbreaks at the beginning of the study were removed from the analysis, this left only 10 in the HSV episode group, and 6 in the no episode HSV group,

and therefore the numbers were fairly small. Also, whilst the 6 who did not develop an episode in the *immediate period* following the baseline measures, they had indicated that they had suffered from at least one episode recently. The whole relationship between stress and illness cannot be clearly demarcated into cause and effect. Even if there is evidence for the role of psychosocial factors in preceding illness onset there is also likely to be an after-effect of the illness (i.e. the illness itself causes feelings of negative mood, stress and anxiety). This can be seen in the broad differences between the illness group as a whole and the control group and may account for the somewhat less robust differences within the group and consequently the differences between those suffering more recurrences in the diary period..

7.29 Total Stress, Negative Mood, Negative Events and Mood

The weekly measures of stress, mood, negative events and hassles were summed over the diary period to give a measure of total weekly stress and mood over the period. It can be seen from this analysis that the HSV group were reported significantly higher levels of stress, negative mood and negative events over the diary period compared to the healthy control group. The same differences were considered within the HSV group for those having a recurrence of HSV during the period and those not having a recurrence and it was found that those experiencing an episode of HSV reported significantly higher levels of perceived stress over the period than those not having an episode. Whilst they were also higher in negative mood the difference did not quite reach significance. These findings indicate higher perceived stress and negative mood in the HSV group as a whole, but in particular in those having an outbreak of HSV; whether this is a consequence of having a recurrences of HSV or a precedent to it was not clear though this question was addressed in the next set of analyses.

7.30 Do Weekly Scores Predict an HSV Recurrence the Following Week?

There appeared to be an increase in perceived stress and negative mood in the week prior to an outbreak of cold sore (see Figures 6 and 7). The significance of this was then further analysed by looking at whether there was a significant difference in the stress scores the week prior to a recurrence of HSV between those (a) participants who had a recurrence of HSV the subsequent week and (b) those who did not, and then removing from the analysis those who had had a recurrence of HSV in the week prior to the stress measure in order to remove the possible confounding effect of 'stress after an outbreak'. The differences in stress scores were significantly higher prior to an outbreak even when taking these after-effects into consideration. The same analysis was carried out for both negative mood and negative life events. The difference in negative mood, however, did not reach significance. . This was an interesting finding, given that measures of mood appear to have been found to predict HSV occurrence in previous studies (Shah & Button 1998) more so than psychosocial stressors. However, more transient mood states and objective stress measures are not necessarily the best measures of emotional distress, as Kemeny et al (1989) found. They reported that chronic depressive affect resulted in HSV recurrence but not acute changes in depressive mood. They argued that shorter term mood changes are not sufficient to effect immunosuppresion. In this study perceived levels of how stressed individuals felt may be considered a better measure of emotional distress than transient mood state or objective life events. Whilst there was a trend for negative mood and negative events to be higher prior to an outbreak of cold sores, the only significant differences were for stress and cold sore outbreak. However, the trend was in the expected direction for mood.

As well as considering the relationship between stress and recurrence of HSV, the recurrence of other infectious illness was analysed in the same way. A significant relationship between stress and illness recurrence was also demonstrated. There was a significant difference in the stress scores

the week prior to the development of other infectious illness compared with the week prior to no illness. This analysis, then, provided evidence for the role of stress in preceding outbreaks of HSV as well as in the development of other minor infectious illness.

7.31 Further thoughts on Diary Methodology

The diary methodology used in this study proved to be a good way of investigating the recurrence of infectious illness and changing patterns of stress, negative mood and health. The drawbacks associated with self-report measures can in part be mitigated by the visual verification of symptoms (i.e. in this case the appearance of a cold sore). The problems of self-report are particularly problematic in retrospective reports of health and symptoms, whereas in diary studies such as this participants are mostly reporting current symptoms and current stress, negative mood and other measures as and when they are experiencing them. When asked to recall symptoms, participants' reports are notoriously coloured by how they might be feeling at the time of reporting. This methodology therefore reduces this type of bias. Furthermore, although participants were required to retrospectively report some aspects of health such as the frequency of previous illness, those who were ill at the time of reporting were excluded from the analysis and responses were controlled for the potential influence of negative affect.

The evidence for the relationship between psychological factors and HSV recurrence to date is mixed and as Shah & Button point out in their review of the literature on HSV, "The evidence linking psychological factors to HSV recurrences is based largely on studies in which subjects reported retrospectively on stressful life events, psychological factors and HSV recurrence." (p.7). This study provides evidence for this relationship in a longitudinal, prospective design overcoming many of the methodological weaknesses reported earlier.

7.32 Application of this Methodology to the Study of Chronic Fatigue Syndrome (CFS)

It was felt that this would not only be a good methodology to investigate recurrence of infectious illness but also to investigate the pathogenesis of chronic illness. In the earlier investigation of Infectious Mononucleosis (IM) attempts to recall patients with this chronic illness in order to study its progression over time proved problematic. The cross sectional analysis of those suffering from IM indicated that it would be interesting to consider the pathogenesis of this type of chronic illness. Evidence for the existence of a fatigue syndrome following IM has been supported by research such as that conducted by White et al ((1995). A significant number of patients suffering from Chronic Fatigue Syndrome report that their illness was triggered by IM. By using this diary methodology it would be possible to track the changes in chronic illness over time with participants reporting weekly changes in physical and psychological wellbeing. In the next study the focus was on the pathogenesis of chronic illness and the recurrence of infectious illness in Chronic Fatigue Syndrome (CFS). In particular the aim was to study those CFS patients whose illness had been precipitated by the Epstein Barr Virus, (the virus which causes Infectious Mononucleosis). Any differences between CFS patients with Epstein-Barr virus (i.e. glandular fever) onset and those with 'other onset' CFS were firstly identified and then the pathogenesis of this disorder was further investigated using this diary methodology.

CHAPTER 8

8.1 The Role Of Psychosocial Factors In The Pathogenesis Of Chronic Fatigue Syndrome and susceptibility to recurring viral infections

8.2 Introduction

Research described earlier in this thesis considered the role of psychosocial factors in the onset and progression of Infectious Mononucleosis (i.e. glandular fever). In particular, it considered the following issues: (a) failure to recover from the acute condition; (b) the differences in symptoms and psychological well-being between a healthy control group and those suffering from glandular fever; and finally, (c) also between those in the acute stages of glandular fever and those who had been diagnosed with the illness more than 6 months prior but had still not fully recovered from the illness (i.e. chronic sufferers).

Important cross-sectional differences were identified between the chronic glandular fever sufferers and the control group as well as differences between those in the acute stages. Due to a number of difficulties in conducting a longitudinal study of students suffering from glandular fever it was not possible to address issues associated with the role of psychosocial factors in the progression of the chronic condition. Evidence for a fatigue syndrome following glandular fever, and the significant overlap between chronic fatigue syndrome and chronic glandular fever, supported the idea that it would be useful to investigate these issues in those suffering from Chronic Fatigue Syndrome (CFS).

The debate regarding the role of Epstein Barr Virus (EBV) in the development of CFS was briefly discussed earlier in the thesis; in summary, a number of differing views and contradictory evidence was identified. The most recent convincing evidence suggests that a fatigue syndrome does exist following glandular fever. Over 40% of the glandular fever patients suffering from CFS at 2 months after the illness compared with only 4% of Upper Respiratory Tract Infection (URTI) patients; at 6 months (i.e. when CFS is said to begin)

10% of the glandular fever patients were suffering from the fatigue syndrome compared with 0% of the URTI patients. (White, Thomas and Clare 1995). Further evidence of the role of EBV in CFS will be reviewed later in this chapter when considering theories of aetiology.

This study aims to investigate the role of psychosocial factors in CFS sufferers and in particular to identify the role of psychological stress in the recurrence of fatigue in CFS patients and in the recurrence of other infectious illness. The first issue to be addressed in this analysis was the issue of aetiology. It was necessary to firstly identify whether there were any differences between CFS patients whose illness was precipitated by EBV and those whose illness was precipitated either by other viruses or other, non-viral, factors. In order to investigate any differences associated with aetiological factors an analysis of 236 CFS patients attending Cardiff CFS Clinic was conducted to identify any potential differences. This is described in full in Section 8.15. The diary methodology used in the cold sore study (see Chapter 5) proved to be a suitable way to track changes in psychological stress and illness over time and it was decided to adopt this method to study changes over time in the chronic fatigue patients.

The aim of this introduction is to:

1. Provide a brief background to the issues and controversies surrounding CFS, its aetiology and diagnosis.
2. To briefly discuss issues associated with the definition and epidemiology of CFS.
3. To review evidence regarding the aetiology and psychopathology of CFS.
4. To provide a rationale for the study of the role of psychological factors in the recurrence of fatigue as well as the recurrence of viral infections in CFS.

8.3 Brief History of CFS

Over time, many different names have been given to the illness (or type of illness) now generally referred to as 'Chronic Fatigue Syndrome' (CFS); the main and most enduring characteristic of which is severe and prolonged fatigue. A very brief, historical review of fatigue-related illnesses gives an idea of both the complexity of the illness and the controversies surrounding it. These difficulties have been problematic for both sufferers of this condition as well as those researching this illness.

George Beard, a neurologist, was one of the first to define a fatigue-related illness which was given the name 'Neurasthenia' in 1869. It was believed to be an illness of the nervous system characterized by extreme exhaustion, both physical and mental; the main symptoms were exhaustion, headache, gastrointestinal disturbances and other subjective sensations. After lengthy investigations over many years and continued failed attempts to identify the organic origins of this disorder, interest in the illness started to wane. The diagnosis of Neurasthenia eventually became replaced with the psychiatric diagnosis of 'Psychoneurosis' and the extreme fatigue, typified in this illness, became associated with anxiety-type and/or depressive disorders. By 1960 the term Neurasthenia had been completely dropped from DSM-III, although it still appears in the International Classification of Diseases (ICD-9 and ICD-10). The nature of the disease has continued to be debated but other definitions and diagnoses were developed which largely replaced the earlier term, Neurasthenia.

Other illnesses defined over the years with symptoms in common include: (a) Fibromyalgia, (b) Myasthenia, and (c) Neuromyasthenia. More recently the term Myalgic Encephalomyellitis (ME), has been used to define a fatigue-related illness, although this name implies an etiologic significance which has not been established.

The more recent emergence of diseases associated with chronic fatigue, muscle and joint ache, began in the mid 1950s with an outbreak at the Royal Free

Hospital in London. An epidemic amongst the nursing and medical staff at this hospital occurred and the main symptoms reported here were myalgia, emotional distress and lability, plus unusual motor and sensory symptoms. No obvious physical cause was identified at that time although possible links to Poliomyelitis were later expressed. Eventually the association with Polio was refuted but the notion of an association with infectious illness was muted and this idea has been maintained. There was, it was asserted, 'a strong momentum to reinforce the idea of an organic basis', despite the observation that emotional disturbance was a part of this and other outbreaks.

On the other hand, the argument put forward by McEvedy and Beard (1970) emphasized the psychogenic aspects of this disease, pointing to the climate of anxiety at the time of the outbreak (linked to publicity concerning the threat of polio) and the severe stress to which the staff were subjected at that time. A polarization of opinion continued and to this date there exists proponents of the 'Somatic/Infection Hypothesis' and proponents of the 'Psychogenic Hypothesis'. Research within the Psychoneuroimmunology framework indicates that in this, as well as other, illnesses it is possible to conceptualize the condition in terms of the interaction of both physiological and psychological components as opposed to either one or the other.

Problems associated with changing definitions of this disease and changing names given to this and/or similar disorders probably reflect problems in understanding the disease and its etiology. Theoretical perspectives on etiology revolve around the three main approaches to understanding the disease which are (a) psychological, (b) viral and (c) immunological. In practice these three theoretical perspectives are not mutually exclusive and research continues in all three areas. In line with the development of a biopsychosocial approach to understanding illness in general, more recent research has started to focus on how psychological, viral and immunological aspects of etiology may be inter-related.

8.4 Definition and Diagnosis

The term 'Chronic Fatigue Syndrome' first appeared in the United States in 1988 when the United States' Centre for Disease Control (CDC) were asked to formalize a working case definition for symptoms which had been variously named and attributed to numerous causes since the mid-1800s. After field testing, the case definition was revised and simplified in 1994. This has become known as the 'CDC criteria' or the 'Holmes criteria'. Critics in the UK proposed a new set of criteria in 1991 which became known as the 'Oxford criteria'. The term 'Chronic Fatigue Syndrome' was agreed upon because it is descriptive but does not imply any specific etiology.

The definition of CFS is that it is a disorder characterized by severe disabling fatigue and other symptoms including (a) musculoskeletal pain, (b) sleep disturbances, (c) impaired concentration, and (d) headaches. It continues to be a complex disorder whose key symptoms are: persistent or intermittent fatigue or severe fatigue upon minimal mental or physical exertion. (Sharpe, 1991). Apart from this it is a heterogeneous disorder and patients may complain of a variety of cognitive, muscular, neurological and autonomic symptoms (Dickinson, 1997).

The full diagnostic criteria comparing CDC definition and the Oxford definition is presented in Table 36 below. Differences in the two approaches are apparent. The two important differences between these definitions is that the Oxford criteria requires the presence of mental fatigue whereas the CDC criteria includes a requirement for several physical symptoms, this reflects the CDC emphasis on immunological or infective pathology.

Table 43: CDC and Oxford Criteria for the diagnosis of Chronic Fatigue Syndrome

CDC	Oxford
Clinically evaluated, medically unexplained fatigue of at least six months' duration that is: - Of new onset - Not a result of ongoing exertion - Not substantially alleviated by rest - A substantial reduction in previous levels of activity	Severe disabling fatigue of at least six months' duration that: - Affects both physical and mental functioning - Was present for more than 50% of the time
The occurrence of four or more of the following symptoms: - Subjective memory impairment - Tender lymph nodes - Muscle pain - Joint pain - Headache - Unrefreshing sleep - Post exertional malaise (>24 hours)	Other symptoms particularly myalgia and sleep and mood disturbance may be present.
Exclusion Criteria - Active, unresolved, or suspected disease likely to cause fatigue - Psychotic, melancholic or bipolar depression (but not uncomplicated major depression) - Psychotic disorders - Dementia - Anorexia or bulimia nervosa - Alcohol misuse or other substance misuse - Severe obesity	- Active, unresolved, or suspected disease likely to cause fatigue - Psychotic, melancholic or bipolar depression (but not uncomplicated major depression) - Psychotic disorders - Dementia - Anorexia or bulimia nervosa

(adapted from BMJ Jan 2000).

8.5 Incidence and Prevalence (Epidemiology) of CFS

The approximate incidence of CFS, based upon community and primary care based studies is 0.2-2.6%, depending upon the criteria used (Wesseley et al, 1998). Despite the general belief that a higher prevalence of CFS occurs in the professional classes, population surveys indicate that rates for different socioeconomic groups and ethnic groups are in fact similar (Steele, Dobbins, Fukuda, Reyes, Randall and Koppelman, 1998; Lawrie and Pelosi, 1995). Whilst the typical patient with CFS appears to be white, female and aged 20-50

years, the illness does occur in both men and women of all ages, ethnic and socioeconomic groups (Wessley, 1998). It has been argued, however, that whilst this describes most sufferers who receive a diagnosis, community surveys portray a different picture and the bias may be attributable to differences in access to health care. (Afari and Buchwald 2003).

The prognosis of the disorder is difficult to ascertain due to the fact that information is based largely on patients who attend specialist clinics who are likely to have had the illness longer and may have a poorer outlook. According to Joyce, Hotopf and Wessely (1997), between 20-50% of patients show signs of improvement in the medium term but fewer than 10% return to pre-morbid levels of functioning. The prognosis appears to be better for children and those in primary care. The principal predictors of poor outcome are said to be the intensity of illness beliefs and psychiatric morbidity, however, its prognosis and clear predictors of outcome have not been clearly established. An important feature of this illness is the tendency for relapse to occur, however there is no evidence that the disease is transferable and the illness causes no increase in mortality. CFS probably describes only a percentage of patients who present with chronic symptoms of fatigue.

8.6 Theories of Etiology

Although there is a significant amount of research into the etiology of CFS the precise etiology remains unclear. It has been suggested that 'CFS is in fact a heterogenous syndrome with different pathophysiological anomalies, manifesting with the same or similar symptoms'. "It is a condition of complex and multifactorial etiology" (Afari, 2003, Page 5). Three reasons why research into the etiology of CFS has been problematic are; 1. There is no established biological cause. 2. The heterogeneity of the illness. 3. Difficulties associated with understanding cause and effect relationships in this illness.

The three main theories to be reviewed here are (a) the viral hypothesis, (b) theories associated with immunological vulnerability and (c) the role of psychosocial factors in onset and progression.

8.6.1 The Viral Hypothesis

Many of the patients suffering from CFS have linked the onset of their illness to an infectious episode, so there is a lot of anecdotal evidence for the viral hypothesis. The similarity of the symptoms of CFS to those of some viral infections, in particular Infectious Mononucleosis (IM) also gives some credence to a possible association. Viral illnesses, like fatigue, are fairly common occurrences in people. On average, people are said to experience approximately 3-4 viral infections per year (Couch 1990). People suffering from CFS, however, are highly motivated to find a physical cause for their illness and the potentially confounding effects of such chance associations are high (i.e. when people develop the condition they actively seek out a reason for developing the illness and may attribute causality to an earlier viral illness). It is also psychologically more comfortable to believe their illness is caused by an infection as opposed to having a disorder of psychological etiology. There is some evidence, however, that certain specific viruses have an association with the development of this disorder. The viral illnesses associated with the development of CFS include Epstein Barr Virus (EBV), Q. Fever, Human Herpes Virus 6, and Viral Menningitis. (White, P.D. 2004).

8.6.2 Epstein Barr Virus and CFS

As previously mentioned there have been many reports of an association between chronic EBV infection and the illness. Persistent fatigue after IM has been demonstrated although despite initial optimism regarding the etiologic significance of EBV in the pathogenesis of CFS, opinion in the late 1980s indicated that these earlier findings may have been optimistic for EBV as a cause of CFS (Schooley, 1989; Straus, 1988). More recently, a few important studies have emerged that re-establish the role of EBV in at least a subset of patients with CFS; there is also evidence that a fatigue syndrome exists following IM in at least a subset of sufferers (White et a1995).

Jones et al. (1991) was able to induce B-cell transformation, indicating active infection in about 30% of cases showing the early antigen, compared to

between 5-10% of the control group. However, looking at the characteristics of the viruses involved, they were unable to find substantial differences in the strains of virus between cases and controls, which implies that any deficit may be host- rather than virus-related. Jones (1991) suggested that in a subset of CFS patients, the host immunological surveillance system that suppresses circulating EBV transformed cells may be diminished, permitting reactivation of the virus.

Further confirmation of the role of EBV in CFS, or a similar fatigue syndrome, comes from White and colleagues (White at al., 1995). In these studies, three groups of participants were tested: (a) group 1 with confirmed EBV, (b) a group of controls who had tested negative for EBV and (c) a group recruited by GPs with other viral illnesses not resembling glandular fever, such as URTIs. White found that a fatigue syndrome did exist after glandular fever, they also argued that the fatigue syndrome following glandular fever was both more common than and distinct from depression. It was most common in those with IM, followed by those with illnesses that were clinically similar but actually consisted largely of Adenovirus and Influenza B, confirming an earlier observation made by the authors in another student health center.

The fatigue syndrome consisted of the symptoms of fatigue, retardation, hypersomnia and poor concentration, similar to the ICD-10 definition of Neurasthenia. White compared those with and without a fatigue syndrome on a number of physical variables and found that the presence of cervical lymphadenopathy or pharyngitis on presentation and the absence of EBV CA IgM predicted fatigue 2 months later. By 6 months no physical variable was associated with fatigue but those with a persisting fatigue syndrome were significantly less physically fit when tested at 2 months post illness. Psychological variables assessed retrospectively were only weakly associated with persistent fatigue syndrome but strong associations were noted between pre-morbid variables such as past psychiatric history, introspection and concurrent life events and the development of post-EBV depression.

White then suggests that a fatigue syndrome after EBV infection is a discrete entity, distinct from depression and that the onset of post-infectious fatigue is related to a number of physical variables including the severity of the illness, the nature of the infecting agent and the immunological response. Persistence at 6 months (when CFS is held to begin) is associated with decreased physical fitness and persistence of post-glandular fever depression might be associated with psychological risk factors.

Wesseley and colleagues (1998) noted that enthusiasm for the role of EBV in CFS has ranged from 'enthusiastic espousal to total denial'. Jones and Straus (1987) concluded that whilst it cannot be proven that EBV is a causative factor in CFS, in a subset of CFS patients their immune system involved in suppressing circulating EBV-transformed cells, may be diminished, thereby permitting reactivation of the virus. About 15% of children attending specialist CFS clinics have been found to have evidence of current or recent EBV infection. (Marshall, 1991).

8.6.3 Evidence for the Association between CFS and other Viral Illness

EBV, as mentioned earlier, is a member of the Herpes family of viruses and some research has investigated the role of other herpes viruses in CFS. The role of Enteroviruses have also been investigated; Enteroviruses are RNA viruses and include the Coxsackie, Echo and Polio viruses; about 70 have been identified. The role of Polio, mentioned earlier, prompted the investigation into the role of Enteroviruses in CFS. Again, there has been mixed evidence, Smith and Fox (2000) identified novel Enterovirus sequences in CFS patients similar to a serum sample of a different group of patients with CFS. However, this was not identified in their follow-up study indicating that these Enteroviruses are not likely to be a cause of CFS, but rather that CFS patients may be more susceptible to acute infections by Enteroviruses. The problem is that these Enteroviruses are so common and are usually mild or even innocuous and their incidence is likely to reflect circulating types.

Most of the agents, other than EBV, such as Rubella, Enteroviruses, Herpes viruses (e.g. HHV6) and Retroviruses have not been found to be important in subsequent research either because of methodological problems or because it has not been possible to replicate the findings. Nevertheless, the link with viral infections continues to be a hotly debated issue. CFS may not be due to any persisting infection, despite a range of infectious agents being associated with the disease. (Staines 2004) Evidence suggests that a post-viral syndrome exists after IM and other severe viral infections, even if persistence of an infectious agent in all suffers has not been demonstrated.

8.6.4 Immune Status

Anything that may be related to both viral infection and chronic fatigue might explain the apparent association between viral infection and CFS, clearly immune status is a potential mediating factor. Immune status can lead to an "amnestic response" in which titers of antibodies to a wide variety of agents will rise non-specifically. This has been found in relation to EBV (Holmes et al, 1987), Cytomegalovirus, Human Herpes Virus, Herpes Simplex and Measles (Landay et al, 1991) but not others (Buchwald, 1996). This antibody production may indicate reactivation of latent virus or it could reflect some alteration in the regulation of immunoglobulin production

There is evidence that the occurrence of common viral infections is higher in CFS suffers than controls (Smith, 1999). Given the fact that exposure to such viruses are unlikely to be higher than in the general population, this supports the view that it may be immunosuppressive factors in the host that is the critical factor. Acute infection may lead to CFS via sustained immunological activation or dysregulation, rather than through persistent infection. Smith and colleagues (Smith, Thomas, Borysiewicz and Llewelyn 1999) reported that CFS patients reported significantly more colds and influenza over a 10-week diary period than controls although whether this reflected increased susceptibility to colds or differences in symptom reporting was not established in this study. Further research by Smith and Fox (2000) however included objective measures of illness severity and infection and found that CFS

patients were more susceptible to acute infections, and that this was not due to biased reporting. They also found that the infections suffered by CFS patients did not appear to influence the subsequent clinical state of the patients. Although there have been a number of studies of the immune system, few consistent differences in immune function have been reported.

8.6.5 Psychosocial Factors

If it is the case that CFS patients are more susceptible to acute viral infections and that immunosuppression in CFS patients may be important factors, then it follows that psychological stress may play a role in both its etiology and persistence. There is a significant body of evidence supporting the relationship between psychological stress and increased susceptibility to infectious disease (e.g. Cohen & Williamson, 1991; Cohen, Tyrell & Smith, 1991; Kiecolt Glaser and Glaser, 1987). Earlier in the thesis it was found that psychological stress predisposed to recurrence of Herpes Simplex Virus (HSV). This psychological vulnerability has been found to be independent of symptom reporting or illness behaviour. Evidence from the HSV study suggests that those with chronic HSV infection (i.e. frequent recurrences of cold sores) experienced greater stress, and that this greater stress was associated with both the recurrence of cold sores and the recurrences of other infectious illnesses.

A number of researchers suggest that the etiology of CFS is psychological rather than physical. A number of psychiatric conditions have been associated with CFS, including somatization disorder (Shorter 1993), hyperchondriasis (Manu P., Afflect G, Tennen H. & Morse P.A. 1996), and in particular, major depression (Greenberg D.B., 1990). It is well established that people with CFS suffer co-morbid psychiatric disorders in particular depression and anxiety. Research on the relationship between psychological stress and the development and/or progression of CFS is more limited although a recent large-scale community study found that those who were significantly fatigued and/or psychologically distressed before being diagnosed with a viral infection were more likely to go on to develop chronic fatigue or CFS at 6-months follow-up. Getting a viral infection did not in itself predict chronic fatigue but

psychological distress was associated with subsequent post-viral general symptoms such as headache, malaise, fatigue etc., although not with local symptoms such as cough, sore throat, runny nose etc (Wesseley et al., 1995).

In considering specific psychosocial variables, depression has been consistently associated with CFS. There appears to be a high degree of co-morbidity between CFS and depression. Wessely and colleagues (1999) emphasised the importance of psychological factors in influencing recovery from CFS suggesting that beliefs, attributions and fears were important in the progression of the illness (i.e. the prognosis was less favourable when patients made catastrophic statements about their condition, attributed their illness solely to physical factors such as viral infection rather than to stress or psychological factors, and those with mood problems had a tendency to amplify somatic sensations).

A review of neuroendocrine studies conducted by Komaroff (1994) consistently found abnormalities in the hypothalamic-pituitary adrenal (HPA) axis and Scott, Svec and Dinan (2000) identified serotonin pathways suggesting an altered physiological response to stress in CFS patients. Findings regarding cognitive impairments in CFS have been reported and these include attention, memory and concentration difficulties (Hall 1996).

Partly because of the failure to find any clear cut physical causal factor in CFS, it has been suggested that it is primarily a psychiatric disorder, in particular associated with major depression (Abbey S., 1993). There is certainly an increased prevalence of major depression compared with other chronically ill people or healthy comparison groups (Wessely, Cheder, Hirsch, Wallace and Wright 1995). White (1996), however, found that depression following EBV was distinct from fatigue and associated with pre-morbid social adversity. Wessely, Hotopf and Sharpe (1999) suggest that psychological factors may influence recovery from the illness and patients with mood problems may amplify somatic symptoms, worry more about activity related symptoms following a viral illness and reduce activity. This reduced activity has been associated with a poorer prognosis. Furthermore, Wessely et al found that

when patients make catastrophic statements about their illness or attribute illness to physical factors such as viral illness, their prognosis is less favourable.

The role of psychological stress in the development and progression of CFS whilst having received considerable attention has not been clearly elucidated. Just because psychological correlates are prevalent in CFS, it does not necessary follow that they are causally related. Many studies have found that CFS patients experience significantly higher levels of objective and subjective stress (Hall, 1996) and patients themselves frequently report that their illness is associated with stress (both in terms of onset and weekly changes in the recurrence and severity of CFS-related symptoms). Wilson, Hickie, Lloyd, Hadzi-Parvik, Boughton, Dwyer and Wakefield (1994) state that illness attitudes and coping styles were more important predictors of long term outcome in CFS than any immunological or demographic factors and they argue that more attention should be given to the role of psychological factors in the progression of CFS. There certainly appears to be a need for a greater understanding in the role of psychological stress in the progression of this disorder including the causal relationship between psychological stress and the recurrence of symptoms of fatigue as well as the relationship between stress and the recurrence of other viral illness in CFS patients.

8.7 Methodological Issues in Studying CFS

One of the difficulties identified in the study of IM was the problem of tracking students with chronic illness over time. The diary methodology identified in the study of HSV patients proved to be a successful way of tracking changes over time. This methodology will be adopted in this study to investigate changes in stress and illness in chronic fatigue patients over time.

Researchers to date have not been able to identify a single causal agent in CFS and many now believe that a single cause will not be found because a number of different causes are operating and the identification of these will lead to a number of subgroups of patients. This may not, as some might assume, fall

neatly into psychological or physical causes. There is some evidence emerging that dividing subjects by mode of onset has some merit. Alternatively, CFS may be a single discrete disease but with a number of risk factors, similar to other chronic conditions such as coronary heart disease. The pattern or combination of risk factors may vary from individual to individual but the disease outcome remains the same.

These risk factors are likely to include the variables reviewed earlier (i.e. viral infection, immune function or dysfunction, psychosocial factors such as stress, and psychiatric disorder such as mood and anxiety problems). As risk factors, these variables may overlap and there may be bi-directional influences between them.

A review of the literature in these fields indicated that further research into the role of psychological stress in the pathogenesis of CFS is needed. Furthermore, there are a number of methodological issues which need to be taken into consideration. These included:

1. Lack of control groups in studies, and in particular control groups matched for important confounding variables such as comparable lifestyle and activity levels as well as other health behaviors.
2. Lack of studies considering the potential confounding influence of Negative Affect in self-reported symptoms and psychological well-being.
3. The need to compare different categories of CFS patients in terms of 'onset'.
4. Further confirmation of some previous research findings is required, such as the recurrence of common viral infection in CFS.
5. More specifically there is a lack of longitudinal studies tracking changes in psychological variables, illness variables and recurrence of infectious illness over time.
6. There is also a lack of studies specifically considering the role of psychological stress in recurrence of symptoms of CFS and in the recurrence of other infectious illness in CFS patients compared with controls.

These limitations are taken into consideration in the present study.

8.8 Aims of the Study

The first aim in this study was to consider any differences between EBV onset CFS and other onset CFS.

8.9 Difference between EBV Onset and other Onset CFS

The first consideration in this study was to investigate any differences between those CFS patients whose illness was precipitated by EBV and those whose illness were *not* preceded by EBV. The results of this analysis will be outlined before describing the methodology and the demographics of the sample because it is fundamental to the rest of the investigation. If there were differences between the CFS patients with EBV onset and those with other onset CFS then the study would have to treat the groups separately whereas if there were no reported differences between these groups then issues of etiology in CFS can be disregarded for the purposes of this study and differences between the combined CFS group and the control group could be investigated.

In order to make comparisons between EBV-onset chronic fatigue patients and non EBV-onset chronic fatigue patients, information from the data of patients attending the CFS clinic in Cardiff who had participated in previous research projects was utilized. CFS patients attending this clinic are referred from a Primary Health Care setting and are given a full clinical/biochemical examination. In order to reach a diagnosis of CFS, any other potential causes of fatigue are excluded. Once diagnosed these patients are invited to join a research panel and participation in any research project is optional.

8.10 Aims of the Analysis of CFS Onset

1. To compare those CFS patients with EBV onset (i.e. those patients who specified that their illness was precipitated by glandular fever (EBV virus)) with CFS patients whose illness onset was not preceded by glandular fever

(i.e. all the other CFS patients), to investigate whether there were any differences between these two categories of CFS sufferers on a range of relevant variables including demographic factors, medical/physical factors and psychological measures.

2. To compare CFS patients with EBV onset with CFS patients whose illness was preceded by any *other* type of viral illness, to investigate whether there were any differences between these two categories of CFS sufferers.

8.11 Method (comparison of EBV Onset and other Onset CFS)

The data collected from these patients contained information regarding the onset of CFS as well as information on demographic factors and health behaviors. Measures of the relevant, psychosocial variables were also recorded in these datasets. This information was utilized to consider the possible differences between groups reporting different causal or onset reasons for their illness.

In the next set of tables the results of these comparisons are presented. The tables provide information on *a.* demographic variables, *b.* health behaviors, *c.* general health and symptoms, *d.* personality characteristics, *e.* mood, *f.* depression, *g.* stress and *h.* social support. Analysis of co-variance were conducted to investigate any differences between the male and female EBV onset CFS patients and the male and female Non EBV onset CFS patients. Age was co-varied in this analysis in order to investigate whether a: there were differences between these groups on the above variables and b. whether these differences were confounded by either age or gender. In total 37 variables are analyzed in this section so it might be anticipated that some chance, significant differences would be expected.

8.12 Sample (for comparison of EBV and other Onset CFS.

There were 236 CFS patients in this analysis, 199 EBV onset CFS and 37 with other onset CFS. There were 70 males and 166 females in the sample, which

included 58 males and 141 females with other onset CFS and 12 males and 25 females with EBV onset CFS.

Tables 45, 46, and 47 show mean scores and standard deviations for the variables, comparing the following groups:

Table 44: Definitions of CFS categories and Numbers in each category

Non-EBV Male n=58	These are the male CFS patients whose illness was precipitated by something other than Glandular Fever i.e. non EBV
Non-EBV Female n=141	These are the female CFS patients whose illness was precipitated by something other than Glandular Fever i.e. non EBV
EBV onset Male n=12	These are the male, CFS patients whose illness was precipitated by Glandular fever (EBV).
EBV onset Female n=25	These are the female CFS patients whose illness was precipitated by Glandular fever (EBV).

Table 45: Mean (sd) for EBV onset CFS and other onset CFS patients on demographic variables and health behaviours, co-varying age and gender

Variable	Non-EBV Male N=58 Mean (sd)	Non-EBV Female N=141 Mean (sd)	EBV onset Male N=12 Mean (sd)	EBV onset Female 25 Mean (sd)	Signifi-cance
Age	48.6 (10.8)	52.9 (11.1)	54.8 (11.6)	58.2 (12.6)	n.s.
Health Behaviours: **a. Sleep (hours/night)**	7.2 (0.2)	7.7 (0.2)	8.1 (0.5)	7.2 (0.4)	n.s.
Diet:How often do you eat the following food? 0=never / 4=everyday. **breakfast**	2.94 (1.26)	3.24 (1.2)	3.0 (1.35)	3.36(1.1)	Age= P<0.01
Fried food **0=never / 4=everyday.**	1.41 (0.77)	1.02 (0.8)	1.50 (0.8)	0.60(0.7)	Sex = P<0.0000 Age= P<0.02
Fruit **0=never / 4=everyday.**	4.24 (1.35)	4.66 (1.3)	4.33 (1.3)	3.80(1.4)	n.s.
Regular drinker (y/n)	37% (0.52)	20% (0.4)	50% (0.53)	33%(0.5)	n.s.
Smoker (y/n)	13% (0.35)	21% (0.4)	17% (0.39)	12%(0.3)	n.s.
Number smoked	8.56 (6.19)	15.06(11.7)	10.0 (7.07)	4.33(2.1)	n.s.
Sport **0=never, 2=sometimes 3= frequently.**	0.05 (0.39)	0.43 (0.4)	0.33 (0.89)	0.36(1.0)	n.s.

8.13 Summary of Health Behaviours

Overall there were few significant differences between the EBV onset and non EBV onset CFS patients. There were no significant differences in age across the groups. Largely the health behaviours were similar with few differences in hours slept, healthiness of diet, smoking, being a regular drinker and participating in sport. Older people were more likely to eat breakfast regularly

and older males were more likely to eat fried food, although generally levels of fried food eating were quite low overall

The next table considers the differences between these groups in general health, symptom reporting and fatigue related symptoms.Chi Square analyses were calculated to assess differences between the groups in symptoms.

Table 46: Table to show mean scores for male and female, Epstein Barr onset and other onset CFS. (chi square).

Variable	Non-EBV Male N=58 Mean (sd)	Non-EBV Female N=141 Mean (sd)	EBV onset Male N=12 Mean (sd)	EBV onset Female 25 Mean (sd)	Signi-ficance
Overall physical symptoms in past month	23.0 (9.1)	26.0 (8.4)	23.3(8.3)	25.1 (8.3)	n.s.
Current state of health 1=Worse than ever to 5=Almost completely recovered.	2.8 (1.1)	3.0 (0.9)	2.6 (1.0)	3.4(0.9)	n.s.
Current Symptoms: a. Physical weakness	76 % (0.4)	84% (0.4)	84%(0.4)	72%(0.5)	n.s.
b. Excessive fatigue	79 %(0.4)	85% (0.4)	83%(0.4)	72%(0.5)	n.s.
c. Loss of concentration	93% (0.3)	89% (0.3)	83%(0.4)	80%(0.4)	n.s.
d. Loss of Memory	74% (0.4)	79 %(0.4)	50% (0.2)	68%(0.5)	Age= P<0.002
e. Allergies	22% (0.4)	39% (0.5)	58%(0.5)	40%(0.5)	n.s.
Profile of Fatigue Related Symptoms: a. Somatic symptoms	53.7(23.2)	54.8(19.1)	49.2(17.7)	56.2(17.2)	n.s
b. Fatigue	62.2(15.7)	63.8(16.4)	63.6(14.9)	60.3(17.2)	n.s.
c. Cognitive difficulties	44.98(15.9)	47.18(17.4)	40.0(16.5)	46.8(16.6)	n.s.
d. Emotional difficulties	46.75(19.9)	47.77(22.1)	40.08(19.0)	57.92(23.6)	Sex= P<0.03

8.14 Summary of Symptoms and P.F.R.S

The above table shows that there were few significant differences between the EBV onset CFS patients and the other onset EBV patients in current state of health, overall physical symptoms or fatigue related symptoms. There was an effect of age on memory and there was an effect of gender on emotional difficulties, however, apart from these two factors the groups were well matched on these variables.

In the next table ANCOVAS were calculated to assess differences in personality characteristics, mood and depression, perceived stress, life events, hassles and social support between

Table 47: Mean (sd) for Male and Female, EBV-onset CFS and other onset CFS patients on psychosocial variables, co-varying age

Variable	Non-EBV Male N=58 Mean (sd)	Non-EBV Female N=141 Mean (sd)	EBV onset Male N=12 Mean (sd)	EBV onset Female 25 Mean (sd)	Signi-ficance
Trait Anxiety	48.7 (11.1)	50.4 (11.8)	45.4(10.3)	52.7(11.1)	Sex=0.03
Self esteem	58.9(13.4)	56.3(16.8)	66.2(11.3)	52.4(15.7)	Sex=0.01, age=0.006
Positive Mood	25.9(10.5)	26.0 (9.9)	29.08 (10.1)	22.36 (9.2)	n.s.
Negative Mood	23.0 (9.7)	23.9 (12.1)	22.3 (12.2)	28.0(12.4)	n.s.
Depression (BDI)	15.8(8.3)	16.1(8.5)	12.1(6.1)	16.4(8.7)	n.s.
Perceived Stress	24.7(8.2)	27.7 (8.4)	22.1 (8.6)	27.8 (7.6)	n.s.
Negative Life Events	1.59 (1.8)	2.6 (2.4)	1.25 (1.7)	3.08 (2.2)	Sex 0.001
Positive Life Events	0.93(1.4)	0.8 (1.1)	1.2 (2.0)	0.8 (2.0)	Age P< 0.05
Total Life Events	2.5 (2.3)	3.4 (2.8)	2.4 (2.4)	3.8 (2.4)	Sex P<0.03
Hassles: a. Cumulative severity.	39.3(31.7)	49.9(36.7)	41.0(58.5)	47.2(26.7)	n.s.
b.Frequency	24.1(18.3)	27.2(19.1)	19.2(19.8)	25.88(14.6)	n.s.
c. Intensity	1.6 (0.4)	1.8 (0.4)	1.8 (0.6)	1.8 (0.5)	n.s.
ISEL A	30.5(7.0)	33.9(5.9)	32.3(5.2)	34.3 (4.3)	sex=0.03
ISEL T	34.3(5.6)	35.7(4.3)	36.7(3.7)	36.2(3.4)	ns
ISEL S	27.8(5.3)	28.2(4.6)	32.2(3.9)	29.2(4.4)	Ebvgf P<0.001
ISEL B	31.01(7.0)	33.0(5.4)	35.0 (94.5)	34.5 (4.9)	Ebvgf P<0.009

Ebvgf = Epstein Barr (glandular fever) onset CFS patients.

8.15 Summary of Psychosocial Variables

Again there were very few important differences between the groups on personality characteristics, mood and depression. Males were significantly higher in self esteem than females and there also appeared to be an effect of age on self esteem. Females were higher in trait anxiety than males.

There were very few differences between the groups on measures of objective and subjective stress and social support. There were differences between the EBV onset and other onset CFS patients in two of the social support sub-scales, namely ISEL S which is social support self esteem and ISEL B (belonging sub scale) social support.

For almost all the measures investigated there were no significant differences between those CFS patients with EBV-onset and those with other-onset CFS. There were some gender differences on the measure indicating that females are higher on life events, emotional difficulties and trait anxiety, they were lower in self esteem. The only differences found between the EBV onset and non EBV onset glandular fever patients were the on the two social support sub-scales. In general, however, the groups were not significantly different on a wide range of measures of health behaviors and psychosocial factors and this suggests that the groups do not differ along these variables. Given the number of variables examined in this analysis it would be expected to find some differences by chance. It would be appropriate to consider the glandular fever-onset CFS patients together with the CFS patients whose illness was not precipitated by glandular fever in a study considering the role of psychosocial factors in the progression and recurrence of illness.

The analysis which compared EBV-onset with other viral illness-onset produced very similar results to those above with no significant differences between the groups on a range of relevant measures.

This study, described below, compares a group of patients with CFS with a matched control group. Issues arising out of the literature review are investigated; more specifically it sets out to examine the following issues:

8.16 Specific aims of the Cross-Sectional Analysis

Whilst the overall aim of this study was primarily concerned with the role of psychological stress in precipitating chronic fatigue symptoms and recurrence of viral infection in CFS patients, the cross-sectional analysis largely replicated the glandular fever analysis reported in Chapter 3, as well as replicating previous research by Smith (1990) White (1998) and Buchwald (2000). This analysis investigated physical and psychological consequence of Glandular Fever. It compared the CFS group as a whole, with a control group of healthy participants on:

1. Demographic variables and health behaviors to ensure that any differences between the groups are not biased due to differences on these factors.
2. General health status and symptom perceptions including fatigue, somatic symptoms and cognitive difficulties as well as reported frequency of infectious illness in the previous 12 months. This confirmed the current profile of CFS patients and confirmation of the anticipated differences in symptoms and infectious illness between CFS patients and controls.
3. Psychological measures including life events and psychological stress, depression and negative mood and dispositional characteristics including self esteem, and optimism. This confirms the anticipated psychological profile of CFS patients as reported in studies by Smith (1990) and Buchwald (2000) as well as highlighting similarities and/or differences between the chronic glandular fever patients described in the earlier chapter of this thesis.
4. The use of coping strategies and perceived availability and use of social support.

8.17 Aims in the Longitudinal/Diary Study

The aims in the longitudinal study were to investigate the recurrence of infectious illness over the diary period, comparing CFS patients with healthy controls on the frequency and severity of recurrences of infectious illness and recurrence of symptoms of CFS. The effect of infectious illness on symptoms of CFS was also considered.

The aim was also to develop the understanding of the role of infectious illness in CFS patients further by replicating, where appropriate, the analysis conducted in the diary study of HSV sufferers reported in Chapter 5, with the CFS patients. The HSV study considered the relationship between the psychosocial measures and subsequent recurrence of illness, measured weekly using a diary methodology. This methodology was demonstrated to be an effective way of measuring changes in variables such as stress and illness on a weekly basis to enable the tracking of these changes over a 16-week period. This study looked specifically at the temporal relationships between weekly measures of stress, mood and weekly hassles and the subsequent development of illness (e.g. did high levels of stress/mood/hassles in the previous week increase the likelihood of illness in the following week?).

This study similarly aimed to consider the effect of weekly stress, mood, negative events and coping on subsequent development of infectious illness as well as the effects of these variables on the recurrence of weekly symptoms of CFS, in particular chronic fatigue.

8.18 Specific Aims

In the longitudinal analyses the following specific analyses were conducted:-

1. Scores on weekly measures were summated over the diary period; CFS sufferers were expected to be significantly higher on total weekly measures of stress, negative mood, negative events, frequency of infectious illness and symptoms than the control group over this period.
2. The differences between the CFS group and the control group on frequency of illness were considered, after co-varying trait anxiety and previous illness.
3. Comparison of the severity of symptoms in colds and flu suffered by the CFS patients and the control group, controlling for the number of infections experienced during that period.
4. Investigation of the relationship between baseline psychosocial measures and subsequent illness during the diary period in both the CFS group and the controls. It was expected that CFS patients higher on baseline psychosocial measures would suffer more frequent infectious illness recurrence during the diary period than those low on baseline psychosocial measures.
5. Investigation of the above relationship between baseline psychosocial measures and subsequent infectious illness but taking into consideration the possible confounding effects of previous illness and trait anxiety.
6. To compare those CFS patients suffering frequent infectious illnesses over the diary period with those suffering few recurrences on: (a) total weekly stress, (b) total weekly mood, and (c) total weekly negative events.
7. To investigate the above in the healthy control group.
8. To investigate week by week recurrence of psychosocial stress, mood, incidence and severity of infectious illness and other illness as well as changes in general health and symptom perception over a 15 week period.
9. To investigate the temporal relationships over the period of study, of weekly stress and: (a) the occurrence and severity of viral infections, (b) occurrence and severity of other illness, and (c) severity of fatigue associated with CFS.

10. This part of the analysis will analyze the effect of infectious illness on CFS symptoms and importantly how the outbreak of infectious illness and symptoms may be related to levels of stress in the week prior to the development of that illness.
11. To investigate the temporal relationships over the period of study, of weekly mood and negative events and: (a) occurrence and severity of viral infections, (b) occurrence and severity of other illness, and (c) occurrence of symptoms associated with CFS (severe fatigue).

8.19 Method

8.19.1 Design

A 15-week diary study was conducted measuring the weekly incidence and severity of viral infections, other illness and medication, together with weekly measures of health behaviors, stress and mood, general health, negative and positive events and occurrence of symptoms. The diaries were kept by a group of CFS patients and a non-CFS control group. This methodology was adapted from the methodology used in the Herpes Simplex Study which proved to be an effective way of collecting information regarding changes in psychological and physical variables over time.

8.19.2 Recruitment of Participants

Volunteers in the CFS group had previously attended the Cardiff CFS Clinic and were volunteers from the Cardiff CFS research panel. Patients attending this clinic were given a full examination whereby a full clinical history was taken and the major features of the disease were assessed together with the standard clinical and biochemical investigations. Patients in the sample had been formally diagnosed as suffering from CFS using the Oxford criteria.

The control group were, where possible, either partners or friends of the patients; however, to increase the number of participants in the control group, volunteers were selected from the 'research volunteer pool' at the University

of Bristol. Having partners of the patients as controls ensured that lifestyles of the control group were as similar as possible to the patients (NB: although because more of the patients were female this meant that more of the controls were male).

8.19.3 Participants

The following table describes the age, education level and marital status of the participants in this study.

Table 48: Demographic Characteristics Of CFS Patients and Controls

	CFS Patients	Controls	Sig.
Gender	4 males 17 females	10 males 6 females	
Age	mean = 50 mode=46 range 29 - 77 years	mean = 49.6 mode = 45 range = 34 - 75	n.s.
Marital Status: Married Single Divorced Widowe	 13 58% 3 14% 3 14% 3 14%	 12 75% 1 5% 3 20% 0	n.s.
Education Level: Primary Secondary 'O' levels 'A' levels graduates	mean = 3.33 1 4% 7 33% 7 33% 1 4% 5 26%	mean = 4.31 0 1 7% 6 37% 4 25% 5 31%	n.s.

8.19.4 Summary of Demographics

Chi square analysis revealted no significant differences in the age, marital status and education levels of the two groups. There were more males in the control group than the CFS group due to the use of partners as controls. Having more females in the sample of CFS patients represents the demographics of CFS, which affects more females than males. Earlier analysis also confirmed very few gender differences in the variables under investigation.

8.19.5 Procedure

Participants were contacted by telephone and those who agreed to participate were sent information regarding the study in the post. They were sent a questionnaire booklet which included questions that measured demographic factors (e.g. age, marital status, education, etc), questions on general health and medical background, (NB: and for the CFS group their current health status in relation to CFS), and finally, questions on health-related behaviours were also included.

8.19.6 Measures

The same baseline psychosocial measures that were used in the previous Glandular Fever Study were selected for use in this study. The rationale for the selection of these measures was described earlier in the thesis. The use of the same measures ensured standardization across studies and allowed comparisons to be made both with the earlier glandular fever findings as well as with findings from other studies.

8.19.7 Stress Measures

1. The Life Events Scale
2. Daily Hassles Scale
3. The Perceived Stress
4. The Beck Depression Inventory

5. The Positive and Negative Mood Scale
6. The Life Orientation Test (LOT)
7. Trait Anxiety
8. The Multidimensional Health Locus of Control Scale.
9. The Self Esteem Scale
10. The Ways of Coping Questionnaire
11. The ISEL Social Support Scale
12. The Profile of Fatigue Related Symptoms

All the above scales are fully described in Chapter Two. They are the same scales that were used in both the Glandular Fever Study and the Herpes Simplex Study.

The above measures allow cross sectional differences between the CFS patients and the healthy controls to be made and also the relationship between baseline measures and subsequent illness.

The next set of measures aims to track changes in psychological variables, illness variables and recurrence of infectious illness over time.

8.19.8 Weekly Measures

Patients were given a set of 15 weekly diary questionnaires which they were asked to complete on the same day of each week for 15 weeks. These weekly questionnaires took approximately 10 minutes to complete and measured the following factors:

1. Incidence of infectious illness that week (and type of illness)
2. Incidence of other illness that week
3. Medication
4. General health
5. Sleep quality
6. Alcohol consumption
7. Exercise

8. Stress
9. Mood
10. Occurrence of negative and positive events
11. Coping
12. Specific symptoms and severity of symptoms

If they had suffered an illness there were further questions regarding the severity and impact of the illness, its length and treatment of illness; there was also a further symptom checklist. Patients returned the weekly questionnaires in stamped, addressed envelopes as soon as they were completed. Patients and controls were very efficient at completing and returning the questionnaires and there was little requirement for telephone reminders. (see Appendix A2.17 for a copy of the Diary Questionnaire).

8.20 Results

The first table considers basic differences between the CFS participants and the healthy control group on measures of health, recurring infectious and other illness, past illness, allergies and medication.

Table 49: Differences Between The CfS Patients and The Control Group on measures of health and previous illness

	CFS Patients		Controls	
	N	%	N	%
Ever diagnosed with E.B.V	6	29%	1	6%
Suffer from recurring illness or infections.	11	55%	1	6%
Major past illness	7	33%	0	
Allergies	11	55%	2	14%
Medication:				
Prescribed drugs	13	62%	4	25%
Over the counter drugs	10	48%	1	6%
Vitamins & minerals	13	62%	4	25%

8.21 Summary of Demographics and Health

The groups were matched on the demographic variables of age, education and marital status. The control group largely comprised partners of the CFS participants. The reason partners were selected was to increase the likelihood that the control group would have similar lifestyle and health behaviours although there are also limitations, one of which is that this leads to a gender imbalance in the controls. Gender differences were considered earlier in the thesis and overall the decision was taken to include partners as controls in this study.

The CFS sufferers took more medication than controls, both prescribed and over-the-counter and also took more vitamins. It is probably understandable that the CFS patients take more prescribed and over the counter drugs as well as vitamins, however, consideration needs to be given to whether the drugs could influence results in any way. The CFS patients suffered from more recurring infectious illnesses as anticipated. A full clinical profile of CFS patients and their current symptoms are given in the next set of tables. The fact that the groups did not differ on demographic variables and health behaviors ensures that in subsequent analyses these variables do not confound the results.

8.22 Clinical Profile of the CFS Patients

The next table gives a breakdown of the CFS patients current health, the duration of their illness, its severity and what they believed precipitated their illness.

Table 50: Clinical Profile of CFS Patients

Duration of illness	**Mean 124.85 months**	**10.4 years Range=1 month to 240 months**
Current severity of Illness?	Worse than at any stage	0
	Bad	3 (15%)
	Bad with some recovery	7 (33%)
	Recovering with occasional relapses	9 (43%)
	Almost completely	

	recovered	2 (9%)
Did an event or illness precipitate the onset of CFS?	Yes = 18 (90%)	
What event or illness? **a. influenza** **b. Sore throat** **c. Glandular Fever** **d. Severe stomach upset** **e. Stress** **f. Other**	 Yes = 6 (32%) Yes = 8 (42%) Yes = 3 (16%) Yes = 2 (11%) Yes = 13 (68%) Yes = 6 (31%)	

8.23 Summary, Clinical Profile of CFS Patients

This table shows that there was a wide range in length of time since developing CFS. Some were very recently diagnosed and others had been suffering with the illness for 20 years. Most of the sample indicated that they were 'bad with some recovery' or 'recovering with occasional relapses'. Most of the sample (90%) believed that there was an event or illness which precipitated CFS and the majority of them suggest that it was Stress (some indicated more than one factor). Many of them also believe that it was an infectious illness of some type that triggered their CFS. The next table provides a breakdown of the symptoms currently suffered by CFS patients, compared with controls as well as the perceived severity of those symptoms.

8.24 Incidence and Severity of Symptoms

Table 51: Incidence and Severity of Symptoms in CFS patients and Controls

Symptom	CFS Patients		Healthy Controls	
	% yes	Mean (sd) severity++	% yes	Mean (sd) severity++
Physical weakness **	21 (100%)	2.8 (1.3)	5 (32%)	1.5 (0.7)
Excessive fatigue **	21 (100%)	3.2 (1.4)	5 (32%)	1.6 (0.7)
Legs feel heavy **	18 (86%)	2.6 (1.2)	3 (19%)	1.3 (0.4)
Muscle Pain *	15(72%)	2.5 (1.2)	8 (50%)	1.6 (0.9)
Pain in Chest	8 (38%)	1.6 (0.9)	2 (12%)	1.2 (0.5)
Painful Joints *	16 (76%)	2.5 (1.2)	5 (32%)	1.4 (0.7)

Nausea *	14 (67%)	2.1 (1.1)	1 (6%)	1.1 (0.3)
Indigestion *	12(57%)	2.1 (1.2)	2 (12%)	1.1 (0.3)
Bloated stomach **	17 (81%)	2.6 (1.2)	0	1.0
Wind **	16 (76%)	2.5 (1.2)	6 (38%)	1.4 (0.6)
Sore throat **	11 (52%)	2.1 (1.2)	4 (25%)	1.3 (0.4)
Headache *	15 (71%)	2.6 (1.3)	5 (31%)	1.6 (0.9)
Earache	6 (29%)	1.3 (0.6)	1 (6%)	1.3 (0.5)
Sore Eyes *	15 (71%)	2.2 (0.9)	2 (12%)	1.1 (0.3)
Sensitive to noise *	17 (81%)	2.5 (1.2)	2 (12%)	1.1 (0.3)
Sensitive to light *	14 (67%)	2.4 (1.3)	0	1.0
Feeling hot/cold **	18 (86%)	2.9 (1.3)	2 (12%)	1.3 (0.7)
Sweating *	14(67%)	2.3 (1.2)	3 (19%)	1.3 (0.6)
Shivering *	15 (71%)	2.3 (1.3)	1 (6%)	1.1 (0.3)
Swollen glands **	8 (35%)	1.7 (0.9)	1 (6%)	1.1 (0.3)
Racing heart	12 (55%)	1.7 (0.9)	1 (6%)	1.3 (0.5)
Insomnia **	15 (71%)	2.5 (1.1)	3 (19%)	1.4 (0.8)
Depression *	12 (55%)	2.2 (1.2)	3 (19%)	1.3 (0.7)
Anxiety/panic *	15 (70%)	2.3 (1.3)	2 (12%)	1.3 (0.7)
Loss concentration **	20 (95%)	3.0 (1.4)	4 (25%)	1.4 (0.6)
Loss of memory **	17 (81%)	2.5 (1.1)	3 (19%)	1.3 (0.7)
Allergies *	7 (30%)	1.5 (0.7)	1 (6%)	1.1 (0.3)
Other A *	8 (35%)	1.9 (1.2)	0	
Other B *	5 (20%)	1.6 (1.1)	0	

(++severity range= 1not present /2 mild/3 moderate/4 severe/ 5 very severe).

(* = P<0.01; ** = P<0.001)

8.25 Summary

The above table shows that the CFS patients are suffering from the usual symptoms associated with their illness. They also appear to be significantly higher on symptoms associated with infectious illness such as swollen glands, sore throat. The next table provides a breakdown of the symptoms currently suffered by CFS patients, compared with controls as well as the perceived severity of those symptoms.

Table 52: Mean (sd) scores for the Chronic Fatigue Patients and the Control Group on a range of health behaviors

Health Behaviors	CfS patients: Mean (sd)	Healthy Controls: Mean (sd)	Sig.
Hours slept per night	6.7 (1.7)	7.1 (1.4)	n.s.
How often rested? 0=never -.4 v.often	1.4 (0.9)	3.1 (0.9)	P< 0.00
Sleep difficulties	2.8 (1.3)	1.9 (1.4)	P<0.04
Healthy diet 0=v.unhlthy - 4=v.hlthy	2.9 (1.0)	2.6 (0.9)	n.s.
Type of food eaten: 1=never....6=2xdaily			
Fresh fruit	4.3 (1.5)	4.3 (1.3)	n.s.
Fresh veg.	3.9 (0.9)	3.9 (0.9)	n.s.
Fried food	2.2 (0.9)	2.6 (0.9)	n.s.
Alcohol consumption. 0=non drinker 4=regular	1.6 (0.9)	1.9 (0.9)	n.s.
0=light drinker 3=heavy	0.4 (0.5)	0.6 (0.6)	n.s.
Beer last week	2.6 (5.8)	7.9 (13.3)	n.s.
Spirits last week	0.3 (0.7)	2.1 (2.5)	P<0.006
Wine last week	2.1 (3.7)	1.9 (3.1)	n.s.
Smoking. No. of smokers No. of cigarettes	2.2 (5.5)	5.4 (9.1)	n.s.
Exercise frequency: (0=never 2=frequently.)			
Jogging/running	1.0 (0.8)	1.5 (0.8)	P<0.06
Swimming	0.5 (0.8)	0.6 (0.8)	n.s.
Physical work (home)	1.4 (0.6)	1.7 (0.5)	n.s
Energetic Sports	0.1 (0.5)	0.6 (0.9)	n.s..
Non energetic Sports	0.3 (0.7)	0.2 (0.5)	n.s.
Watching t.v.	2.7 (0.9)	2.6 (1.2)	n.s.
			n.s.

8.26 Summary of Differences between CFS Patients and Controls in Symptoms and Health Behaviours

As anticipated, there were large significant differences in reported symptoms between the CFS patients and controls. In terms of health behaviors, there were no differences between the CFS patients and controls in 'healthiness' of diet and the type of food eaten. The amount of sleep was not different but the quality of sleep was impaired in the CFS group compared with controls. There were no differences in smoking or overall alcohol consumption although the control group drank more spirits than the CFS patients. There were no differences in levels of moderate exercise and activity although the controls were significantly higher in vigorous activity and running/jogging. Overall then the groups were matched on important health behaviours except for quality of sleep and vigorous exercise which would be anticipated from the nature of this illness.

In terms of the clinical profile of the CFS sufferers, this matches the anticipated profile of symptoms. Most of the patients were 'recovering with occasional lapses' (43%) or 'bad with some recovery' (33%). Their views on what precipitated their illness shows that stress was perceived to be an important factor although infectious illnesses such as flu, colds and glandular fever were nominated by significant numbers and being important in the onset of their condition. The next analyses considers the incidence of previous infectious illness.

8.27 Incidence and Frequency of Infectious Illness in the past 12 Months

CFS patients and controls were asked to provide information about the incidence and frequency of colds, sore throats, influenza, bronchitis and other illness during the previous 12 months. Anovas were calculated to assess whether differences between the healthy controls and the CFS patients, in the number of report illnesses in the past 12 months was significant. Results are reported in Table 46 below.

Table 53: Frequency of previous illness in CFS patients and controls

	None	Few	Average	A lot	Mean (sd) ++	Sig.
No of Colds						
CFS Patients	-	5(24%)	9 (43%)	7 (33%)	3.1 (0.8)	
Controls	3 (18%)	8 (50%)	5 (31%)	0	2.1 (0.7)	P<0.004
Sore Throats						
CFS Patients	2 (10%)	5(24%)	6 (29%)	8 (38%)	2.9 (1.0)	
Controls	5 (31%)	7 (44%)	4 (25%)	0	1.9 (0.8)	P<0.002
Influenza						
CFS Patients	7 (33%)	3 (14%)	6 (29%)	5 (24%)	2.4 (1.2)	
Controls	11 (69%)	4 (25%)	1 (6%)	0	1.4 (0.6)	P<0.003
Bronchitis						
CFS Patients	13 (62%)	3 (19%)	3 (14%)	1 (5%)	1.61 (0.9)	
Controls	16 (100%)	-	-	-	-	
Other illness						
CFS Patients	15(71%)	2 (10%)	0	4 (19%)	1.8 (1.3)	
Controls	15 (94%)	1 (6%)	0	0	1.1 (0.3)	P<0.03

(NB: mean = mean score where none = 1, few=2, average=3, a lot =4).

8.28 Summary of Reported Illness in the past 12 Months

It can be seen that the CFS patients reported suffering significantly more colds, sore throats, flu and other illnesses during the previous 12 months than the controls. There were no differences between the groups for bronchitis and other illnesses. The next set of analyses in this section considers the differences between the CFS patients and the healthy control group on the baseline psychosocial measures taking into consideration the possible confounding influence of negative affect.

8.29 Analysis of Differences between CFS Patients and Control Groups on Psychosocial Measures at Baseline, Controlling for Negative Affect

Analysis of co-variance (Ancova) were carried out to investigate differences between the CFS patients and the Healthy Controls on the psychosocial measures taken at time one. Negative Affect was co-varied to see whether these differences were in fact a consequence of this potential confounding factor. The next set of tables shows the results of this Ancova for 1. Psychosocial Measures, 2. Fatigue related symptoms, and 3. Social support and coping.

Table 54: Mean (sd) scores for CFS participants and controls on Psychosocial Measures

Psychosocial Variable	Non-CFS Controls N=16 Mean (s.d.)	CFS Patients N=21 Mean (s.d.)	Sig.
Perceived Stress	17.8 (9.3)	27.1 (8.1)	**P=0.002**
Co-vary n.a.	21.4 (1.2)	24.4 (1.1)	P=0.05
Negative Life Events	1.1 (1.6)	2.6 (2.13)	**P=0.02**
Co-vary n.a.	1.4 (0.5)	2.5 (0.4)	n.s.
Total Life Events	1.6 (1.6)	3.0 (2.6)	**P=0.06**
Co-vary n.a.	1.7 (0.6)	2.9 (0.5)	n.s
Hassles-cumsev	18.8 (15.9)	37.2 (28.9)	**P=0.03**
Co-vary n.a.	26.4 (5.5)	31.8 (4.6)	n.s
Hassles-frequency	14.8 (11.7)	22.8 (12.2)	**P=0.05**
Co-vary n.a.	17.5 (2.5)	19.9 (2.2)	n.s.
Hassles-intensity	1.4 (0.5)	1.6 (0.3)	n.s.
Co-vary n.a.	1.5 (0.3)	1.4 (0.2)	n.s.
B.D.I.	6.88 (9.03)	13.81 (5.89)	**P=0.007**
Co-vary n.a.	9.2	12.02	P=0.01
Negative Mood	10.3 (8.9)	20.9 (11.7)	**P=0.004**
Co-vary n.a.	13.9 (2.0)	18.1 (1.7)	n.s.
Life Orientation	33.46 (7.3)	29.0 (7.4)	**P=0.08**
Co vary n.a.	30.8 (1.5)	31.97 (1.3)	n.s.
Self Esteem	61.31 (10.47)	55.24 (12.58)	P=0.12 n.s.

Table 55: Mean (sd) scores for CFS participants and controls on the Profile of Fatigue Related Symptoms

Psychosocial Variable	Non-CFS Controls N=16 Mean (s.d.)	CFS Patients N=21 Mean (s.d.)	Sig.
Fatigue	24.4 (15.6)	53.8 (15.3)	**P=0.006**
Co-vary trait anx.	28.0 (3.8)	51.0 (3.3)	**P=0.0001**
Emotional Difficulty	25.9 (18.7)	41.7 (20.4)	**P=0.02**
Co-vary trait anx.	33.2 (3.5)	36.2 (3.0)	n.s.
Cognitive Difficulty	19.1 (12.0)	40.7 (15.6)	**P=0.0001**
Co-vary trait anx.	27.73.2	37.9 (2.8)	**P=0.001**
Somatic Symptoms	22.9 (11.7)	47.8 (16.2)	**P=0.0000**
Co-vary trait anx.	26.3 (3.4)	45.2 (2.9)	**P=0.0003**

Table 56: Mean (sd) scores for CFS participants and controls on measures of Social Support and Coping Strategies

Psychosocial Variable	Non-CFS Controls N=16 Mean (s.d.)	CFS Patients N=21 Mean (s.d.)	Sig.
Total Social Support	132.9 (16.8)	129.9 (16.3)	n.s.
Co vary n.a.	127.9 (3.4)	133.9 (2.9)	n.s.
Coping strategies			
a. prob.solv	12.7 (4.5)	15.4 (4.0)	P=0.002
Co-vary n.a.	11.6 (0.9)	16.2 (0.9)	P=0.002
b. confronting	11.2 (2.0)	9.6 (2.1)	P= 0.02
Co-vary n.a.	9.0 (0.5)	11.6 (0.4)	P=0.0004
c. seek social support	11.6 (4.6)	13.6 (3.7)	n.s.
Co-vary n.a.	11.2 (0.9)	13.9 (0.8)	n.s.
d. positive readjustment	11.0 (5.5)	14.4 (5.1)	P=0.06
Co-vary n.a.	10.3 (1.4)	14.9 (1.2)	P=0.02
e. accept responsibility	6.7 (2.5)	8.0 (2.8)	n.s.
Co-vary n.a.	6.8 (0.7)	8.0 (0.6)	n.s.
f. slf con	13.5 (4.2)	16.4 (3.5)	P= 0.03
Co-vary n.a.	13.3 (1.0)	16.5 (0.9)	P=0.03
g.Escape Avoidance	11.2 (2.7)	14.7 (4.9)	P = 0.07
Co-vary n.a.	11.9 (1.0)	14.1 (0.9)	n.s.
h. Distancing	10.1 (4.3)	12.2 (2.2)	P = 0.07
Co-vary n.a.	9.6 (0.8)	12.5 (0.7)	P=0.01

8.30 Summary of Analysis of Co-variance

There were large differences between the CFS group and control on the range of psychosocial variables measured. These statistically significant differences were largely, although not consistently, apparent when negative affect was co-varied. The measures which did remain significant after co-varying negative affect were, perceived stress, depression, fatigue, cognitive difficulty, somatic symptoms, and certain coping strategies. The role of negative life events continued to be greater for CFS sufferers but this did not quite reach statistical significance. These findings confirm earlier study findings that, in a cross-sectional study, CFS patients reported higher psychological distress than controls.

8.31 Conclusions of Cross Sectional Study

The cross sectional analysis reported in this chapter confirms that the CFS participants and the controls do not differ significantly on important demographic and life style variables and that any differences between the groups on health and psychosocial measures were not a consequence of differences in health behaviours. The analysis confirms earlier studies such as Smith (2000) of differences between CFS patients and controls on measures of psychological stress and psychological well being and these differences are maintained even when negative affect is controlled. This cross sectional analysis also confirmed the clinical profile of CFS patients in this study and reported on the significant differences between CFS patients and controls on the frequency of other infectious illness.

The next chapter reports on the longitudinal part of this study and considers the role of psychosocial factors in the pathogenesis of CFS and in the recurrence of other infectious illness in CFS patients.

CHAPTER 9

9.1 The Role of Psychosocial Factors in CFS – A Longitudinal Analysis

9.2 The Diary Measures

Weekly scores for general health, stress, mood and coping were summated over the fifteen week period of the diary study and total scores for the period were compared. Lower scores depicted poorer health, higher stress levels, greater negative mood and poorer coping. The next set of Ancovas compared the CFS participants and the Healthy Control participants on these summated diary measures, again taking the possible confounding influence of negative affect into account.

Table 57: Mean (s.d.) scores on diary measures for the CFS patients and controls

	CFS patients Mean (s.d.)	Non-CFS controls Mean (s.d.)	Significance
1. Mean frequency of infectious illness	6.93 (3.95)	0.50 (0.79)	P<0.0000
Co-vary n.a..	6.85 (0.84)	0.64 (0.95)	P<0.05
2. Mean frequency of other illness	4.31 (4.35)	1.33 (4.31)	P<0.09 n.s.
3. Weekly general health*	37.92 (9.43)	55.92 (9.83)	P<0.0001
Co-vary n.a.	39. 01 (2.79)	55.72 (2.55)	P<0.0005
4. Total weekly stress *	39.69 (8.98)	47.42 (8.68)	P<0.05
Co vary n.a.	41.52 (1.95)	45.11 (2.14)	P<0.0005
5. Total weekly mood *	43.62 (5.82)	56.16 (9.45)	P<0.0005
Co-vary n.a.	45.45 (1.51)	54.02 (1.64)	P<0.0000
6. Total weekly good events	3.77 (3.32)	.58 (2.54)	n.s.
7. Total weekly bad events	14.92 (11.02)	3.33 (3.75)	P<0.002
Co-vary n.a.	13.86 (9.31)	2.64 (3.47)	P<0.01
8. Total general coping	43.50 (11.54)	56.42 (11.42)	P<0.01
Co vary n.a.	45.87 (2.31)	54.31 (2.42)	P<0.0000
9. Average weekly symptoms	26.01 (5.84)	17.39 (4.57)	P<0.0000
Co-vary n.a.	24.59 (4.43)	17.79 (3.98)	P<0.0001

* Weekly scores on these variables range from 1 to 5 where 1 = extremely unwell / Extremely Stressful/ Extremely negative). Possible range of scores are 15 to 75. Higher scores = better health, less stress and more positive mood.

Table 57 shows statistically significant differences between the CFS patients and controls on summated weekly measures. They suffered significantly more infectious illness, stress, negative mood and weekly negative events over the diary period. They coped significantly less well and their general health was poorer. These differences were still present when known biases in reporting were controlled. The next table considers differences between the groups on the total weekly symptoms and severity of symptoms. i.e. symptoms /symptom severity reported each week were totaled and the weekly scores of the CFS patients and the controls were compared in the next table.

Table 58: Total weekly reported symptom severity for CFS participants and controls

Total Symptoms	Chronic Fatigue	Healthy Controls	Significance
Week A	27.57 (5.46)	18.19 (3.79)	P<0.0000
Week B	25.50 (5.54)	16.94 (2.74)	P<0.0000
Week C	26.95 (5.13)	17.44 (4.84)	P<0.0000
Week D	26.38 (7.76)	17.88 (4.54)	P<0.0000
Week E	25.57 (5.05)	17.87 (4.57)	P<0.0000
Week F	25.29 (4.92)	17.25 (4.22)	P<0.0000
Week G	26.05 (6.32)	16.69 (3.30)	P<0.0000
Week H	25.91 (4.09)	16.25 (3.02)	P<0.0000
Week I	26.84 (5.33)	16.69 (3.54	P<0.0000
Week J	26.77 (6.23)	16.88 (4.37)	P<0.0000
Week K	26.29 (5.94)	17.07 (4.58)	P<0.0000
Week L	25.06 (4.16)	17.62 (6.02)	P<0.0004
Week M	24.88 (4.77)	19.00 (6.59)	P<0.009
Week N	25.59 (4.90)	17.08 (3.63)	P<0.0000
Week O	25.57 (4.45)	18.08 (5.90)	P<0.0012

NOTE: For each of 16 symptoms participants indicated from 1 (symptom not experienced), 2 (moderate symptom), 3 (extreme symptoms). Range of scores for weekly symptoms were 16 = no symptoms experienced to 48 (16 symptoms of high severity)

The above table demonstrates that the CFS patients, as anticipated, consistently reported suffering from more symptoms of greater severity than the healthy control group. The next table considers the recurrence of infectious illness over the diary period in CFS patients and controls.

9.3 Weekly Recurrence of Colds and Influenza in CFS Participants and Controls

The following figure shows the recurrence of colds and influenza, each week during the diary period for the CFS patients and the Control Group.

Figure 8. Percentage of participants reporting infectious illness (colds and influenza) over the 15 week diary period

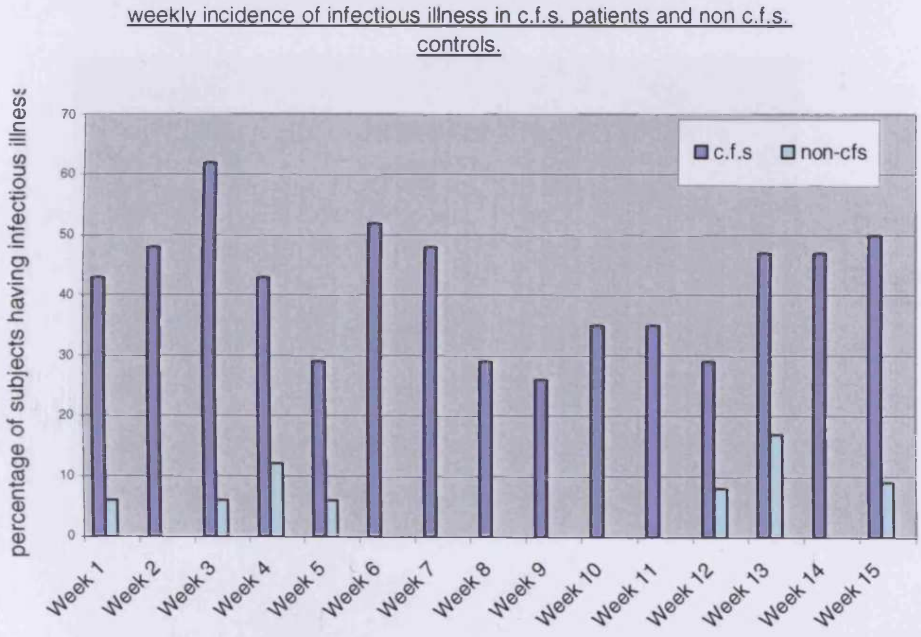


Figure 8 shows the percentage of CFS and healthy control participants reporting an infectious illness each week. It can be seen that the CFS patients reported significantly more colds and influenza infections over the diary period than controls. Anovas were used to calculate the overall difference between the CFS patients and the control group on the frequency of recurrence of infectious illness during the diary period (controls mean =

0.55 (sd 0.82); mean CFS patients 6.929 (sd 3.95), F=27.5, Sig. P < 0.000). Levels of infectious illness in CFS patients in this study are similar to those reported by Smith et al. (1999). The differences between the groups in the frequency of other (non-infectious) illness was not significant (controls mean =1.45 (sd 4.50), CFS mean=4.31 (sd 4.35) f = 2.48, P< 0.13).

The next figure shows the weekly levels of reported stress over the diary period for the CFS participants and the Control Group.

Figure 9. Weekly Stress Scores for CFS Patients and Controls

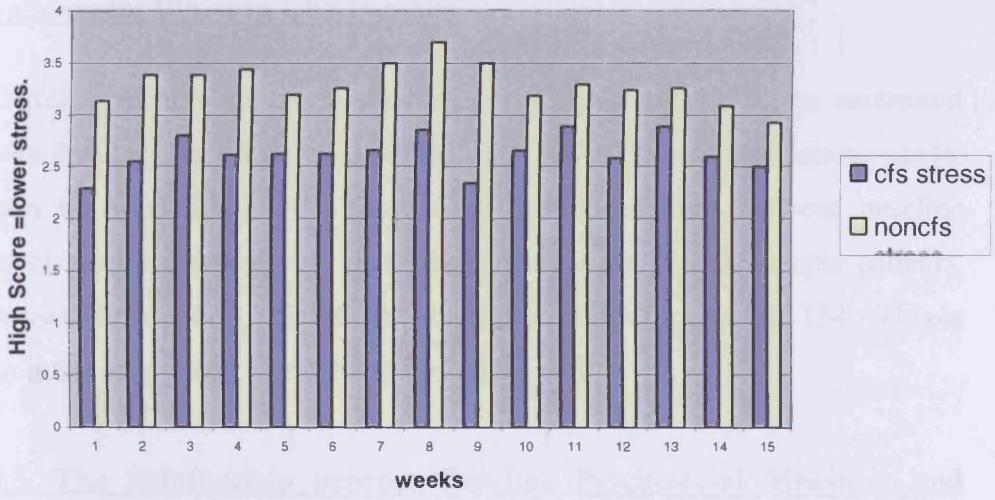


Figure 9, above shows the differences between the CFS patients and controls in weekly measures of perceived stress; the CFS patients were consistently higher in perceived stress than the controls. The overall differences between the groups (significance and s.d) are given in table 50. This figure demonstrates a consistent pattern of higher weekly stress in the CFS patients compared with the controls. Before going on to consider the precise longitudinal relationship between psychological stress and recurrence of infectious illness, the relationship between baseline psychosocial measures and subsequent recurrences over the diary period of (a) infectious illness, (b)

other illness, and (c) weekly mental and physical fatigue were correlated. Whilst the aim was to compare those CFS patients having frequent recurrences of infectious illnesses during the diary period with those having none or few infectious illnesses, there were only three CFS patients having 4 or less infectious illnesses during the diary period and there were few significant differences between those having 4 or less and those having 5 or more illnesses during the diary period on baseline psychosocial measures.. Due to there being insufficient numbers of CFS patients to classify as 'low frequency of infectious illness' a correlational analysis of baseline measures and diary measures was conducted. Diary scores over the 15 weeks of the diary period were summated and correlations between these scores and the baseline measures were calculated.

9.4 The Relationship between Baseline Psychosocial Measures and Subsequent Illness in CFS Patients

Correlations between baseline psychosocial measures and scores summated over the diary period were calculated. The tables of these correlations can be seen in Appendix A3.4. There were few correlations between baseline psychosocial measures and diary measures for the chronic fatigue patients. In total there were 10 significant correlations out of a possible 154. This is no more than would be expected by chance.

9.5. The Relationship between Baseline Psychosocial Measures and Subsequent Illness in the Control Group

Baseline psychosocial measures were more likely to be correlated with subsequent stress and health scores during the diary period in the healthy control group. They were also associated with the likelihood of developing infectious illness during the diary period. These correlations, however, largely disappeared when negative affect was co-varied. (see appendix A3.4 for a complete table of correlations)

9.6 Summary

Overall, it can be concluded that there were very few significant correlations between baseline psychosocial measures and frequency of recurrence of infectious illness or weekly summated scores on other measures in the CFS patients. It was hypothesized that there would be correlations between baseline measures and subsequent recurrence of illness but this did not prove to be the case in the CFS group. It was found that the CFS patients were significantly higher than controls on baseline measures (see Tables 54, 55 and 56) and on subsequent recurrence of infectious illness during the diary period (see Table 57). They were also higher on weekly stress, negative mood, poor general health and negative events during the diary period than the controls (Table 57). The CFS group suffered frequent recurrences of infectious illness over the diary period and it was not possible to easily divide them into high and low recurring infectious illness categories. There were only 2 CFS sufferers who had less than 2 recurrences of infectious illness during the diary period. In fact, nearly all the CFS cases had above average recurrences of infectious illness during this period and whilst they were high on baseline measure and high on subsequent diary measures there did not appear to be the expected significant correlation between these measures. This analysis found that baseline measures of stress and psychological well being were not significantly correlated with subsequent measures of stress, general health and infectious illness.

This was not the case, however, for the control group who had lower baseline measures of stress and lower incidence of infectious illness over the diary period. In this group there was a correlation between baseline measure and subsequent illness. These significant correlations largely disappeared however when negative affect was co-varied. Possible reasons for this will be discussed further after the next analysis which could throw further light on this finding. The next series of analyses considered whether weekly changes in measures of stress and negative mood were associated with recurrence of infectious illness and symptoms of CFS. From this analysis it could not be concluded that stress measures taken at baseline would predict

subsequent illness in CFS patients and whilst it did so in the control group, this relationship was no longer significant when negative affect was co-varied.

9.7 Relationship between Weekly Stress Measures and Subsequent Recurrence of Infectious Illness over the Diary period

This was the final, critical step in the analysis of stress and illness in CFS patients, which looked specifically at the temporal relationships between psychological stress and the development of infectious illness in CFS sufferers; the critical issue was the specific, longitudinal relationship between stress and illness. The measures of stress and illness, which were taken weekly for the 15 weeks of the diary period, were analyzed in the next series of analyses. Scores were calculated for weekly stress in the week prior to an episode of infectious illness and compared with the stress scores in the week prior to *no* infectious illness. This will be referred to as the 'week-by-week' analysis (i.e. scores taken for the week prior to an illness and compared with the scores on the same variable the week prior to no illness). This allowed the tracking of any changes which might have occurred in psychological stress the week immediately prior to an illness developing.

In these analyses the week-by-week stress and (a) infectious illness, (b) other illness, and (c) physical fatigue were studied; these analyses indicated whether stress *preceded* the onset of infectious illness, other illness and physical fatigue, in CFS sufferers.

Stress scores for the CFS patients were calculated the week prior to an outbreak of infectious illness/fatigue. If they were actually ill/fatigued on that week, their scores were not used. The stress scores on the week prior to an illness/high fatigue were compared with the stress scores on weeks prior to no illness/fatigue. Within group T Tests were calculated to investigate whether the differences in stress scores were significant.

The same analysis was also carried out for negative mood (i.e. mood scores the week prior to an illness were examined and compared to mood scores the week prior to 'no illness').

The same set of analyses were carried out firstly for the CFS participants only and secondly for the healthy control group. The following tables shows the results of this analysis firstly for the CFS participants looking at differences in stress scores the week prior to developing an infectious illness, secondly stress scores the week prior to a other illness and thirdly stress scores the week prior to suffering high levels of physical fatigue. The same analysis was then conducted for negative mood scores.

9.8 Results of Longitudinal Analysis

Table 59: Mean (sd) scores for Stress/Mood/symptom in the week prior to illness and the week prior to 'no illness' for CFS Participants

CFS Patients	Prior to illness Mean Value (sd)	Prior to no illness Mean Value (sd)	Sig.
Stress and Infectious Illness:	2.09 (0.46)	3.04 (0.75	P <0.0000
Stress and Other Illness	2.37 (0.82)	2.81 (0.63)	P<0.01
Stress and Physical Fatigue.	2.67 (0.58)	2.45 (0.53)	P<0.000
Mood and Infectious Illness:	2.48 (0.69)	3.07 (0.66)	P0.001
Mood and Other Illness	2.85 (0.73)	2.94 (0.60)	n.s.
Mood and Physical Fatigue.	2.92 (0.46)	2.88 (0.48)	n.s.

Note: low score = greater stress.

9.9 Summary for CFS participants

There were significant differences in stress scores the week prior to the development of an infectious illness compared with the stress scores the week prior to not developing an infectious illness in the CFS patients. There were also significant differences in the week prior to developing 'other illness' compared with stress scores the week prior to 'no illness'. Again, for physical fatigue, stress scores were significantly higher in the week before developing this symptom compared with the weeks prior to not having this symptom.

For negative mood there were significant differences in scores the week prior to developing an infectious illness compared with the weeks before no infectious illness but the differences in mood scores for weeks prior to other illness and physical fatigue were not significant.

The next table shows the results of the same analyses this time looking at these relationships in the healthy control volunteers.

Table 60: Mean (sd) score for Stress/Mood symptom in the week prior to illness and the week prior to 'no illness' for Healthy Participants

CFS Patients.	Prior to illness Mean Value (s.d.)	Prior to no illness. Mean Value (s.d.)	Sig.
Stress and Infectious Illness:	3.21 (1.14)	3.41 (0.67)	n.s.
Stress and Other Illness	2.37 (0.82)	2.81 (0.63)	P<0.01
Stress and Physical Fatigue.	3.35 (0.71)	3.06 (0.62)	n.s.
Mood and Infectious Illness:	3.75 (0.76)	3.83 (0.68)	n.s.
Mood and Other Illness	3.87 (0.74)	3.86 (0.59)	n.s.
Mood and Physical Fatigue.	3.79 (0.61)	3.80 (0.63)	n.s.

9.10 Summary for Healthy Participants

Stress scores in the week prior to developing an infectious illness were not higher than scores in the weeks prior to 'no infectious illness' for the healthy control group, neither were the scores any different in weeks prior to 'physical fatigue' compared with weeks before 'no physical fatigue'. Scores the week prior to developing 'other illness' were significantly higher, however. There were no significant differences in mood scores for the control group.

9.11 The Relationship between Infectious Illness and CFS Symptoms

The same analysis was conducted looking at the relationship between infectious illness and subsequent physical fatigue. There were no statistically significant differences within the CFS group between the levels of fatigue the week following infectious illness compared with the week following no infectious illness. This suggests that infectious illness does not directly influence the symptoms of CFS. This finding confirms the findings of Smith et al (1999) who reported that acute URTIs did not alter the pathogenesis of CFS.

9.12 Summary of Longitudinal Analysis

This series of analyses showed that for the CFS patients, levels of stress fluctuate from week-to-week but there were significantly higher levels of stress in the weeks prior to an outbreak of infectious illness or other illness as well as in the weeks prior to reported higher levels of physical fatigue. It would seem that psychological stress preceded the development of illness in the CFS group. It was interesting that baseline measures of objective and subjective stress did not correlate with frequency of recurrence of infectious illness during the diary period. One reason for this might be that these CFS patients were significantly higher in measures of psychological distress and stress and were also significantly higher in frequency of infectious illness than controls. CFS patients experienced high levels of objective and subjective stress, depression and negative mood in the baseline measures but

this was not associated with frequency of recurrence of infectious illness during the subsequent diary period, whereas weekly fluctuations in stress and negative mood were associated longitudinally with the development of illness. They started off the study by reporting high levels of stress and were characterized by fluctuating levels of stress on a week-by-week basis. It could be that weekly stress, additional to high stable measures of stress and/or distress, puts the CFS patients at risk for the development of infectious illness and symptoms of CFS, namely increased physical fatigue.

It is possible that day to day stress, additional to high baseline levels of stress, operates in a cumulative manner and tips the balance in CFS patients rendering them vulnerable to the immunosuppressive effects of high stress and the subsequent development of illness. Associated with the weekly changes in stress and negative mood was the subsequent development of infectious illnesses. Other explanations for this relationship between increased stress and subsequent development of illness and fatigue could be the mediating health behaviours – although generally there does not appear to be significant differences between the CFS patients and controls; alternatively stress could be associated with the perception of illness and reporting of symptoms, although again this possibility was reduced by including measures of negative affect.

The scenario for the control group was different insofar as for the control group, baseline measures were initially more likely to be associated with subsequent infectious illness. This relationship largely disappeared however when negative affect was co-varied. For the control group, there were infrequent recurrences of infectious illness generally and those who reported higher baseline measures of psychological stress also reported more infectious illness during the diary period but this was probably a consequence of high levels of symptom reporting in this group due to the effect of higher negative affect. This was similar to the finding of the earlier study of cold sore sufferers when once again the healthy controls in this group reported higher stress and higher infectious illness but the relationship also was influenced by negative affectivity. The healthy control group were

less affected, however, by weekly changes in stress and did not report higher levels of stress in the week prior to developing an infectious illness.

9.13 Discussion

Overall, the findings of this study reveal that in terms of the general profile of CFS cases, it does not really matter whether the illness was precipitated by EBV or any other virus. The issue of etiology was addressed in the initial analysis by comparing two groups of CFS patients, namely those whose illness was precipitated by EBV and those whose illness were not precipitated by EBV. There were very few significant differences (less than would be expected by chance given the number of anovas conducted) in the current profile of CFS patients that were distinguished by differences in the reason for onset of the illness. Demographics and health behaviours were compared, as well as general health and current symptoms, and no significant differences were found between CFS patients with EBV-onset (or other viral illness) and those whose illness were precipitated by psychological stress and/or other factors.

Furthermore, there were very few differences in a wide range of relevant psychosocial measures between these two groups of CFS patients. This analysis suggests that whilst there may well be different reasons why people develop this disorder, and these may include viral illnesses and/or psychological stress, the pathogenesis of the disorder is similar regardless of the factors precipitating illness onset. This study relied upon patients' self-reported reasons for illness onset and, as mentioned earlier, people may be motivated to attribute causality to some physical factor such as a severe viral illness. If this is the case, the classification into different types of onset may just be an artifact. However, glandular fever (as discussed in an earlier chapter) is a severe and disabling illness very different from other viral illnesses which occur frequently and recurrently. People who define their illness as glandular fever are likely to have been diagnosed by a medical practitioner and may be more confident in associating the onset of CFS with this illness. The idea that a particular chronic condition may have a range of

risk factors associated with its onset is not a new or revolutionary notion. Coronary Heart Disease (CHD), the major cause of death in Western Society, has a number of precipitating factors including genetic, behavioural (smoking and alcohol consumption) and psychological (stress and type A behaviour) risk factors. The symptoms and progression of CHD are not associated with which factors are caused its development (i.e whether it was caused by lifestyle or genetic factors) and this could be the same for CFS. There may be a range of reasons why people develop this chronic condition but this does not allow us necessarily to categorize them or make predictions regarding the prognosis of the disorder. EBV may well be a risk factor for the development of CFS, on its own or in combination with other risk factors. However, as far as this study is concerned, the lack of differences between the patients with different precipitating factors means that it is reasonable to place all those suffering from CFS into one category for analysis.

The control and CFS groups were compared on a range of demographic variables and health behaviours to avoid confounding factors influencing possible differences between the groups. There were no significant differences between the groups in age, education level and marital status. There were slightly more females in the CFS group but this was a consequence of using partners of patients in the control groups. Using partners had the advantage of matching lifestyle factors between the groups but the disadvantage of influencing the gender balance. One other disadvantage of using partners is that living with a partner suffering from a chronic illness such as CFS might increase levels of stress amongst that group. Further studies should consider the issue of control groups and the further possibility of having a control group suffering from another chronic condition to identify whether or not stress is related specifically to CFS or more generally to the recurrence or perpetuation of other chronic conditions.

In terms of health risk behaviours, the groups were matched on diet, alcohol consumption, smoking, general exercise and amount of sleep. The control group, as might be expected, had a better quality of sleep than the CFS

patients and took more vigorous exercise such as jogging and energetic sports. Overall, it was concluded that any differences between the groups would not be a consequence of health and lifestyle factors.

The clinical profile of the CFS group was in line with the anticipated profile of those suffering from this illness. They took more medication than the control group, both prescribed and over-the-counter and more vitamins. The current severity of the illness in the CFS patients ranged from 15% who were 'bad' and 9% who were almost completely recovered; the majority of patients were recovering with occasional relapses (43%). There were significant differences between the two groups in the number and severity of symptoms. As would be expected, the CFS patients suffered more of the symptoms related to CFS than controls. There were also significant differences between the groups in the incidence and frequency of other infectious illnesses in the previous 12 months. CFS patients reported that they suffered significantly more colds, sore throats and flu than the control group over the previous year.

Overall, this study confirms the findings of previous research which had found large significant differences in the psychological well-being of CFS patients compared with the healthy controls. The differences between the groups on measures of objective and subjective stress, mood/depression, fatigue-related symptoms and coping strategies were highly statistically significant. Most of these significant differences were maintained when trait anxiety was co-varied, suggesting that the differences were not simply a consequence of higher levels of symptom reporting in highly anxious individuals. This is an important issue in self-reported measures of this kind which are frequently taken at face value. The fact that the differences between the groups remained after taking negative affectivity (n.a.) into consideration avoids the possible biased reporting associated with this personality profile.

The psychosocial profile of the CFS patients was very similar to that of the glandular fever patients reported in Chapter 3. In fact, the scores were most

similar to the glandular fever patients in the chronic category (as might be expected). There appears to be significant overlap between the profile of chronic, symptomatic glandular fever patients and CFS patients in this study.

The cross-sectional results then support research findings regarding the physical and psychological status of those suffering from CFS. These findings do not, however, tell us anything about the direction of the relationship between these psychosocial measures and illness. Do people with CFS suffer increased stress, depression as a consequence of their illness or is the stress and depression associated with the development and progression of the illness? The answer to this question remains illusive. Certainly CFS may be a consequence of severe infectious illness, such as glandular fever, and a psychiatric history predicts increased risk of depression in patients suffering from a post-viral fatigue syndrome (White, 1995). The longitudinal analysis considered both the changes in the illness over time, the frequency of other infectious illnesses and their role in CFS as well as the direction of the relationship between psychological stress, infectious illness recurrence and CFS symptoms.

9.13.1 Longitudinal Study

The longitudinal analysis tracked changes in the CFS patients over a 15-week period. Changes in stress, mood, negative events, general health, symptoms of CFS, and recurrence of infectious illness and other illness were tracked over this period and the nature of the relationship between these variables were investigated.

First of all, the total scores were summated over the diary period. This enabled a comparison to be made between the CFS patients and the control group during the diary period. It was found, as expected, that overall there were significant differences between the groups on most of the variables measured. The CFS group suffered from statistically significant greater number of infectious illnesses during the study period; the CFS group reported weekly measures of psychological stress and negative mood that

were statistically significantly greater than the control group. The control group experienced overall better general health and felt more in control of events (i.e. coping) than the CFS patients. The CFS patients reported more negative hassles than the controls. These identified differences were maintained when negative affect was statistically controlled.

Comparisons were also made between the CFS and control groups on the total weekly symptoms reported, and the CFS patients reported a statistically significant greater number of symptoms each week than the control group.

In the next series of analyses, the relationship between baseline psychosocial measures and subsequent recurrence of illness was investigated. There were very few significant relationships between the baseline measures and subsequent illness in the CFS cases. This was partly due to the overall high incidence of infectious illness in the CFS groups generally; there were only two CFS sufferers who had less than two recurrences of infectious illness in this group which made it very difficult to make a sensible division between high- and low-levels of infectious illness groups. When the groups were divided into those having '5 or more' illnesses and those having '4 or less' and compared statistically, there were no significant differences between levels of subsequent infectious illness. This division, whilst allowing for sufficient numbers in the 2 categories to make a comparison possible, could not be considered to reflect a division into high- and low-frequency occurrence (NB: having 4 weeks of infectious illness out of 15 was not a low incidence). Similar problems were experienced with the control group who suffered few recurrences of infectious illness; it was not feasible to divide the control group into high- and low-frequency recurrence of illness groups due to the overall low frequency. For this reason correlations were considered for (a) the CFS cases and (b) the control group separately.

There were very few statistically significant correlations for the CFS cases; for the control group there were many highly statistically significant correlations between the baseline and subsequent diary measures (including the frequency of recurrence of infectious illness and other illnesses over the

diary period). The possible reasons for the difference between the baseline measures and subsequent weekly incidence of infectious illness was discussed earlier. In summary, it appears that whilst the CFS group scored higher on the baseline, stable, psychosocial measures of psychological stress and distress (NB: and also higher on weekly recurrence of illness and infectious illness) it is not the baseline measures which predict the actual onset of the infectious illness for CFS patients; it would appear that rather this group are 'tipped' over the edge by weekly fluctuations in state measures of stress i.e. 'how stressed are you *this week*?'.

9.13.2 Weekly Changes in Stress and Illness

The most important findings of this study were the changes in the levels of weekly stress and negative mood and their impact on the recurrence of infectious illness, fatigue symptoms and other illnesses over the course of the diary period. These analyses demonstrated that stress scores for CFS patients were higher in the week prior to infectious illness compared to weeks prior to no infectious illness; the same relationship was also demonstrated for the severity of physical fatigue. It would appear from these data that there is an association between perceived stress and recurrence of infectious illness in CFS patients. This finding confirms previous research by Smith and colleagues (1999) that CFS patients suffer more frequent recurrences of infectious illness than healthy people

The association between perceived stress and the incidence of infectious illness has been demonstrated in studies by Cohen, Tyrell and Smith (1991). These studies were conducted in strict laboratory conditions where careful controls for exposure to virus were possible. Cohen and colleagues demonstrated that there was a 'dose-response relationship' between psychological stress and infectious illness whereby higher levels of stress were associated with an increased likelihood of infectious illness. This relationship between psychological stress and infectious illness would appear to be mediated by immune function.

As well as supporting earlier research on the recurrence of infectious illness this study also demonstrated that the recurrence of illness is preceded by high levels of stress and negative mood. This increase in perceived stress and negative mood directly preceded the development of illness in the CFS patients.

They were higher on trait measures of psychological distress but it was the weekly fluctuations that predicted the development of an infectious illness. The study also found a relationship between stress and subsequent severity of physical fatigue (one of the main symptoms of CFS). Whilst infectious illness did not appear to influence the pathogenesis of CFS (i.e. physical fatigue was not higher in the week following an infectious illness than it was in the week following no illness) it did appear that one of the main symptoms of CFS, fatigue, was precipitated by the occurrence of higher levels of weekly stress. It could be the case, however, that the physical fatigue is simply associated with the development of infectious illness. So, whilst stress precedes infectious illness and physical fatigue, the physical fatigue may simply be a symptom associated with illness rather than the recurrence of CFS.

For the control group the baseline psychosocial measures also predicted increased likelihood of developing illness, however, weekly fluctuations in stress and negative mood did not appear to be associated with the development of an illness.

It can be concluded that those suffering from CFS were subject to higher levels of psychological stress compared to healthy controls and this psychological stress was directly associated with recurrence of infectious illness and recurrence of the symptoms of chronic fatigue. This relationship between stress and illness, mediated by the immune system, indicated that the pathogenesis of CFS is characterized by ongoing high levels of stress, immunosuppression and subsequent recurrences of infectious illness and fatigue-related symptoms.

Earlier attempts to distinguish between psychogenic causes (e.g. anxiety and depression) and organic causes (e.g. viral illness) were predicated on a bio-medical model of illness emanating from Germ Theory; Germ Theory suggests that for any condition there must be a pathogen which invades the body and causes an identifiable cluster of symptoms which medical practitioners can identify, label and subsequently treat. The more recent Biopsychosocial model of illness challenges this notion and emphasizes the intricate relationship between mind and body. This model suggests that for almost any illness there is some combination of physiological and psychological factors in its onset and progression and this contrasts with the view that illness may be *either* psychological or physiological. The Biopsychosocial model explains the interaction of psychological and physical factors in the onset and/or progression of illness (Engle, 1977). This model of health/illness may be more associated with the concept of risk factors for the development and progression of illness, as opposed to identifying a pathogen or single physical cause. It appears to be a more appropriate model for understanding the sort of chronic conditions that many people commonly suffer from now.

The relationships between many of the variables identified in this study are likely to be multi-directional. Negative mood and depression will influence behavioural factors such as the quality-of-life and the engagement in normal daily activities. Inability to conduct normal activities will be associated with increased levels of psychological stress and inability to cope adequately; failure to recover from infectious illness is likely to increase negative mood and increase perceived stress. This may influence the immune system rendering the person more vulnerable to other infectious illness and exacerbating the symptoms of the illness. For CFS patients there is a constant downward spiral of continuing high levels of stress, frequent weekly fluctuations in stress followed by the development of infectious illness and symptoms of fatigue. One of the challenges for research in this area is to untangle these complex inter-relationships.

9.14 Conclusions

The final study in this thesis demonstrated high levels of negative mood and psychological stress in CFS patients. CFS patients also suffered a statistically significant greater number of recurrences of infectious illness compared to the control group. The recurrence of infectious illness as well as the severity of the symptoms of physical fatigue was preceded by high levels of weekly stress and negative mood. This study was a progression from the earlier study of Glandular Fever and utilized the same cross sectional measures as those used in the Glandular Fever study. This study further adopted the diary methodology of the study of Herpes Simplex study to investigate the longitudinal relationship between psychological stress and negative mood and the recurrence of both infectious illness in CFS patients and the recurrence of fatigue. The overlap between chronic Infectious Mononucleosis (IM) sufferers and those suffering from CFS provided the impetus to investigate the role of psychosocial factors in the progression of CFS, and given the large numbers of CFS patients with EBV-onset CFS and the lack of any obvious differences between those and sufferers with other-onset CFS; it is logical to assume that the results would be similar for the chronic IM patients. The findings provide support for a longitudinal relationship between psychosocial factors and subsequent recurrence of illness.

The next and final chapter in this thesis summarizes the main findings of the studies reported in this thesis and relates the findings of these studies to previous research which provided the initial rationale for conducting these investigations.

CHAPTER 10

10.1 Overall Summary, Discussion and Conclusion

The fundamental aim of this thesis was to develop our understanding of the role of psychosocial factors in physical illness. In particular to investigate further whether psychological stress, depression, negative mood can influence susceptibility to the recurrence of infectious illness. A number of studies to date have considered the role of psychosocial factors in immune function (e.g. Kiecolt Glaser et al 1984), and whether psychological factors influence immune system mediated disease (Cohen et al 1991, 1993) and these were reviewed in the introductory chapter.

This thesis focused on the role of psychosocial factors in Herpes Virus Infections. Herpes Virus Infections differ from other common viral infections in that after exposure to the virus they remain present, usually in latent state, within the host for ever. One of the reasons for selecting latent viruses was that it overcomes any difficulties associated with controlling exposure to virus. As the cellular immune response is the important factor in preventing latent herpes virus infection from being reactivated, anything compromising cellular immunity will allow reactivation of the virus. It quickly became apparent in the course of studying Infectious Mononucleosis that another interesting avenue to investigate further was the frequency of recurrence of other common viral infections in those with herpes virus and the frequency of recurrence of other common viral infections, such as colds and flu in Epstein Barr onset Chronic Fatigue Syndrome.

In his review of the literature in this field, Cohen and Herbert (1996) concluded that: although the literature is impressive and provides plausible explanations for how psychological factors might influence immunity and immune system mediated disease, many of the relations reported may be attributable to health

behaviours such as smoking, alcohol consumption, exercise etc. and that further studies are required which better control for the effect of these health practices on immune function. The studies in this thesis ensured that health risk behaviours were controlled, as well as addressing a number of other methodological problems in this area of research. The role of negative affect, reported to influencing self reports of health status and psychological well being, was controlled as well as the role of current and past illness in influencing responses regarding current health status. Problems associated with the measurement stress and the need to take into consideration both objective measures of life events and subjective perception of stress were all issues considered in the studies in this thesis.

The thesis was grouped around three main investigations, commencing with the study of Infectious Mononucleosis (Glandular Fever). The second area of research was into the role of psychosocial factors in Herpes Simplex Type 1 (cold sores) and the final study considered the role of psychosocial factors and recurring infectious illness in a longitudinal study of Chronic Fatigue Syndrome (CFS). The rationale and interest in the study of CFS was initially a consequence of the overlap between Chronic Infectious Mononucleosis and CFS and the first step in this investigation was to investigate any differences between CFS patients whose illness developed from Glandular Fever (EBV onset CFS) and those whose illness had not been preceded by Glandular Fever (non-EBV CFS). The three studies and the main findings are summarised below.

10.2 Infectious Mononucleosis

This was the first topic of interest which fulfilled the criteria of being a member of the herpes family of virus, therefore able to lay dormant and being subject to recurrence. It had the added advantage of being more common amongst young adults and University Students were therefore a suitable population for recruiting those suffering from this illness. It is well established that whilst

Glandular Fever is a severe, debilitating illness, there are large individual differences in how quickly sufferers recover from this illness. Whilst most sufferers recover within six to eight weeks a minority of people with glandular fever continuing suffering from the symptoms for extended periods of time and/or suffer recurrences of the primary symptoms over an extended period of time. This study aimed to investigate the after effects of glandular fever, in particular looking at the perceived effects and progression of the illness and to consider differences in both physical and psychological morbidity at different stages of the illness in particular considering differences between those in the acute stages of the illness with those who had not recovered and whose illness had continued for an extended period of time (referred to as Chronics).

This study confirmed previous research showing high levels of psychological distress in those suffering from Glandular fever. The findings indicated that there were significant differences between Glandular Fever participants and the healthy control group on a range of measures of psychological stress and distress. It was also shown that those who had been suffering from the illness for more than three months continued to be significantly higher than controls on measures of psychological stress and distress although there was a trend for the scores on these measures to decrease over time i.e. they were highest in those in the acute condition and lower in the chronic condition, although still significantly higher than controls. Interestingly, there was no correlation between length of time since diagnosis and perceived severity of the illness so it was not the case that perceived severity decreased over time since diagnosis.

It was noted that not all the chronic glandular fever participants reported that they were suffering from the primary symptoms of the illness (sore throat, swollen glands, high temperature, headache and fatigue) at the time of data collection and comparisons were also made with this group. It appeared from the reports of the progression of the illness that some sufferers experienced a prolonged illness with levels of symptoms maintained over the time. The

majority of those who fail to recover, however, report recurrences of the symptoms with periods of either 'normal' health or near to 'normal' health in between – a more fluctuating type of illness. When comparing the psychological profile of the chronic symptomatic (those appearing to be having a recurrence at the time of testing) and the chronic glandular fever participants not experiencing the main symptoms of the illness at that time, there were few differences in psychological distress indicating perhaps that the symptoms were not the cause of the distress.

Frequency of recurrence of other infectious illness was also measured in this study and it was found that both the acute and the chronic glandular fever participants reported significantly more frequent colds and influenza than controls. There is an overlap between the symptoms of glandular fever and the symptoms of colds and influenza and it is unclear – probably to the sufferers themselves, whether they are actually experiencing a recurrence of the illness or alternatively an infection with another rhino type virus. The fact that they experience such frequent recurrences of infectious illness suggests that their immune systems are in some way compromised thereby failing to effectively combat these other infectious illness. It could be that the high levels of psychological stress and distress experienced by the glandular fever participants is causing this immunosuppression and rendering them more vulnerable to infectious illness and it was hoped to investigate, in a longitudinal study, the progression of the illness and the temporal relationship between psychological stress and distress and either recovery or recurrences of the symptoms of glandular fever as well as the relationship between psychological stress and distress and the recurrences of other infectious illness in this group. Difficulties with the sample made it impossible to do this and so the next studies were planned in an attempt to develop this investigation and look at these longitudinal relationships between psychological stress and distress and the recurrence of illness over time. The second study in this thesis considered the role of psychosocial factors in Herpes Simplex Type 1, a more frequently recurring and

in some ways more easily verifiable recurring infectious illness. The methodology established in the glandular fever study was utilised in the subsequent studies and was supplemented with a diary methodology in order to take more frequent measures of the relevant variables over time for the longitudinal analysis.

10.3 Herpes Simplex Type I (HSV)

There were two parts to this study, a cross-sectional analysis, similar to the glandular fever study summarised above, comparing those suffering from HSV with a healthy control group on a range of measures of psychological stress and distress followed by a longitudinal analysis investigating the causal relationship over time between psychological stress, distress and recurrence of HSV as well as the recurrence of other infectious illness.

In the cross sectional study the first analysis considered differences in measures of psychosocial stress and psychological distress between the healthy control group and the cold sore group and, as anticipated, there were large significant differences between the two groups on all the measures. Interestingly however, when negative affect was co-varied in this analysis the large differences between the two groups all but disappeared. In other words when controlling for negative affect the only remaining significant difference between the cold sore group and the healthy was for depression, suggesting that the cold sore group were not suffering any higher levels of stress than the healthy group. The next analysis took into consideration the role of 'illness severity' and a different picture emerged. There were large variations within the cold sore group in the number of cold sore recurrences experienced - some experiencing one cold sore episode a year ranging up to two cold sore episodes a month on average. Illness severity referred to the frequency of recurrence of cold sores and differences in psychosocial measures between those suffering frequent recurrences and few recurrences were analysed. Both previous illness and

negative affect were controlled in this analysis and significant differences were observed between the high incidence cold sore group and the controls and on measures of psychological stress and distress. There were also some significant differences between the high incidence cold sore group and the low incidence cold sore group. So whilst the differences between the cold sore group as a whole and the control group on the psychosocial measures were no longer significant when the relevant confounding variables were controlled, the differences between the high incidence cold sore group and the healthy controls remained significant. The high incidence cold sore group were the ones suffering high levels of psychological stress and distress and not those who suffered relatively infrequent recurrences of cold sores. They also suffered more frequent recurrences of other infectious illnesses than the low incidence group and the healthy controls. This suggests that this group of participants are highly stressed and distressed, suffering frequent recurrences of cold sores as well as high levels than normal of colds and influenza. This might indicate an immunosuppressive effect of high stress increasing vulnerability to illness. The idea that severity of illness might be an important factor in the relationship between stress and illness has been suggested by Zorilla et al (1996). The alternative explanation which might be drawn from cross sectional investigations such as this, however, is that illness, and in particular severe illness, leads to the experience of psychological stress and distress, therefore, it was necessary to investigate the relationship these variables using a longitudinal design.

In the longitudinal study of cold sores, the aim was to investigate more specific cause and effect relationships between psychological stress, depression, negative mood and the recurrence of cold sores. Diary methodology was utilised to collect weekly information regarding psychological stress and distress, recurrence of cold sores and other infectious illness. Findings supported Hoon (1986) with significant correlations between monthly recurrence of cold sores and negative life events during the diary period although this analysis could not

be considered truly longitudinal. Although the design of this study was longitudinal in that it followed participants over six months taking monthly measures of life events and cold sore recurrence, the significant finding was that monthly life events were correlated with concurrently reported monthly recurrences

Within the cold sore group there were significant differences between those experiencing an outbreak of cold sore during the diary period and those not experiencing an outbreak in that period on psychological stress scores during that period. The differences for mood did not reach significance. This could mean that experiencing cold sores increases stress or alternatively that increased stress increases the likelihood of having a cold sore. There was evidence that baseline psychosocial measures were associated with the likelihood of subsequently developing a cold sore. Those scoring higher on perceived stress, total life events and depression at baseline were significantly more likely to go on to develop both cold sores and other infectious illness during the diary period and this relationship remained significant when previous illness and previous cold sores were co varied as well as negative affect. Although there did initially appear to be a relationship between baseline psychosocial measures and subsequent illness in the control group, this relationship did not hold when negative affect was co-varied. This supports the earlier finding that frequency of illness is an important issue in relation to the role of psychological stress and distress. When people are experiencing frequent recurrences of infectious illness, psychological stress is likely to play a role. When they suffer infrequent (or normal) levels then it is not necessarily associated with psychological stress.

The relationship between severity of cold sores and psychological stress during the diary period, however, was not significant. Severity and length of outbreak is something that may need to be investigated further but in this study was not found to be significantly associated with psychological variables.

This study did find a significant relationship between frequency of cold sore recurrence and the frequency of recurrence of colds and influenza during the diary period. Again this remained significant when previous illness and negative affect were controlled.

The final part of this analysis concentrated directly on whether or not stress and negative mood directly preceded an outbreak of cold sore. It also considered whether stress or negative mood preceded the development of colds or influenza. An important finding in this study was that there were significant differences in the stress scores in the week prior to an outbreak of cold sore compared with the weeks prior to no outbreak of cold sore. This analysis ensured that any after effects of a cold sore were controlled so that if they had experienced a cold sore in the previous week the stress scores for that week were not included. There was no significant relationship between negative mood and subsequent cold sore episode and neither was there a relationship between experiencing any negative event and developing a cold sore.

The same, longitudinal analysis was then considered for the development of other infectious illness in the whole group. There was a significant difference in the stress scores in the week prior to developing an infectious illness compared with the weeks prior to not developing an infectious illness. Again this was significant when those suffering from the illness in the previous week were removed from the analysis. Again, there were no significant differences between negative mood and subsequent infectious illness and neither was there a relationship between negative events and subsequent illness.

The finding that high stress preceded cold sore recurrence was a significant result in this study because many of the methodological issues discussed earlier had been controlled and direct comparisons were made between weeks prior to the development of a cold sore episode and weeks when there was no

subsequent cold sore episode. This was a truly longitudinal relationship between psychological stress and cold sore outbreak.

Having established both the appropriate methodology – both in the glandular fever study and in the longitudinal section of the Herpes Simplex study - the next study planned to utilize this methodology and return to the issue of chronic illness. Having established that psychological stress is an important factor in Glandular Fever and considered the issue of Epstein Barr onset Chronic Fatigue Syndrome, the next study aimed to replicate the study above of Herpes Simplex, this time using a sample of sufferers of Chronic Fatigue Syndrome. The final study in this thesis aimed to consider the role of psychosocial factors in the pathogenesis of CFS, focusing on the longitudinal relationship between psychological stress and negative mood and both recurrence of the symptoms of CFS as well as in the recurrence of other infectious illness in CFS patients.

10.4 Chronic Fatigue Syndrome

The analysis of CFS started off by considering whether there were any differences in the CFS participants between those whose illness had been precipitated by EBV and those who had been precipitated by anything other than EBV. Having established that there were few, if any, important differences between these groups the analysis went on to consider cross sectional differences between the CFS participants and a matched group of healthy controls. The cross sectional analysis achieved the aims of:

a. Confirming the clinical features of CFS patients demonstrating that this was a group of CFS patients with characteristics similar to those demonstrated in other studies.
b. Confirmed the specific psychosocial difficulties associated with CFS.
c. Demonstrated similarities in the psychosocial profile of the CFS patients and that of the chronic glandular fever participants.

d. Controlled for the role of negative affect in influencing reports of CFS patients and controlled for this in the cross sectional analysis
e. Confirmed previous findings of an increased prevalence of the development of infectious illness in CFS patients compared with controls.

The cross sectional analysis was largely confirmatory, supporting previous research by Smith et al (1995) and White et al (1995) into the role of physical and psychosocial factors in CFS and the recurrence of other infectious illness.

The longitudinal study aimed to investigate the temporal relationship between psychosocial factors and the recurrence of fatigue as well as the relationship between psychological stress and distress and the development of infectious illness.

The longitudinal analysis utilized the diary methodology of the herpes simplex study to measure weekly stress, negative mood, negative events, as well as changing symptoms of CFS and the development of other infectious illness.

The overall scores during the diary period for psychological stress, negative mood, negative events, incidence of colds and influenza were summated and there were significant differences between the CFS patients and the Healthy Control group as anticipated.

The most important finding in this study was that levels of psychological stress and negative mood were significantly higher in the weeks prior to developing an infectious illness than in the weeks prior to not having an infectious illness. Psychological stress and negative mood were also significantly higher in weeks prior to recurrence of the main symptom of CFS, namely fatigue. High levels of stress in the CFS patients may be exacerbated by weekly stress which adds to these already high levels of stress and is likely to precipitate the onset of the

symptoms of CFS as well as the onset of other infectious illness. When Cohen et al (1996) assessed stress in terms of both acute and chronic stress of different durations they found evidence to suggest that although acute stress (lasting less than one month) did not alter susceptibility to colds, enduring chronic stress (lasting one month or longer) was associated with greater susceptibility to rhinovirus-induced colds. The longer the duration of the stressor the greater the risk for developing inefectious illness. This supports the view that those with chronic illness, suffering high levels of stress are at an increased risk for the development of infectious illness. The weekly stress experienced 'tops up' existing generally high levels of stress and increases vulnerability to illness. In the healthy groups, and in the low incidence cold sore group for example, they may experience weekly stress but this is more similar to the acute, short term stress described by Cohen and does not, therefore, render the person to an increased likelihood of developing a cold. This may provide an explanation why recent or acute psychological stress precedes illness in the chronically stressed and ill group and not in the others.

10.5 Limitations of the Research

One of the difficulties experienced in conducting the research for this thesis was the recruitment and retention of participants meeting the relevant criteria and willing to participate in the research. Glandular Fever participants were recruited using Posters at three Universities. They were required to have been diagnosed with the illness within the previous twelve months and still suffering from it. They were also required to have had their illness formally diagnosed in order that confirmation of diagnosis could be sought and be willing to give the time required, returning for the longitudinal study. When people are attending clinics for treatment of illness it is easier *a.* to recruit them and *b.* to ensure that they return for follow up appointments. Even though participants were given a financial incentive for participating, it proved quite difficult and very time consuming to recruit significant numbers of people suffering from this

illness and willing to give up their time for research. Presumably if students had been suffering from glandular fever they might have already missed a substantial amount of time from their studies and therefore be less willing to give up any more of it. A reasonable number of participants who met the criteria were recruited into the study but when it was found necessary to define a number of different case definitions, the numbers within each of the categories became less. This would have been overcome by the recruitment of larger numbers. Although significant findings in the cross sectional analysis was established, with greater numbers, the longitudinal study would have been more viable and other types of analysis might have been possible. Recruitment for the cold sore study was somewhat less difficult, it being a less debilitating and more frequently occurring illness. Nevertheless, the need to recruit those currently suffering from recurrences of cold sore was not always easy – many volunteers who came forward had to be excluded because it had been over a year since they had experienced a reactivation of the virus. It becomes apparent why the majority of studies looking at specific illnesses such as these are conducted in Clinics, thereby introducing the bias associated with a selected group of sufferers being studied, but overcoming the difficulties of recruitment.

10.6 Multivariate Analysis

In the introduction I discussed the need in research into stress and illness of this type, to measure a large number of different variables, all of which may impact the stress/illness relationship in some way. I also discussed the notion of conducting multiple regression analysis to assess the relative weight these variables may contribute to the outcomes under investigation. Again, the problem of conducting this type of analysis comes back to the question of the number of participants recruited into the study. With the need for this range of variables, the actual number of participants required becomes almost untenable. Nevertheless, it might be an interesting development in this research to be more restrictive in the number of variable included and consider multiple regression

analysis to assess the relative weight of influence of the different psychosocial variables on illness outcome and in particular to evaluate the mediating or moderating effects psychological measures such as social support and coping strategies.

This study largely used analysis of variance and co-variance to control for possible confounding factors. Correlations and partial correlations were also conducted and for the purposes of the research in this thesis I believe they were suitable and appropriate methods of analysis.

10.7 Physiological Evidence

It is always preferable in studies of infectious illness to have medical verification of illness. Wherever possible this was sought, hence, the confirmation of diagnosis of glandular fever was acquired as well as the visual verification of cold sores. The CFS patients had been diagnosed by a clinician (although this is diagnosis based on symptoms and not on any physical measure). It would also have been advantageous to have virological confirmation of other infectious illness recurrence. This was beyond the scope of this thesis but again, any future replications would be improved if verification of the recurrence of infectious illness could be confirmed.

10.8 Design

A strength of the research in this thesis was the longitudinal methodology. Whilst much of the cross sectional analysis confirmed previous research, there is a shortage of real, longitudinal research in the literature. Even some of the research that purports to be longitudinal, really sums measures over a period of time and may not be considered to be truly longitudinal. The longitudinal analyses in the studies outlined in this thesis developed our understanding of the causal relationships between psychological stress and the development of infectious illness. The need to control for the confounding influence of health

behaviours, negative affect, current and previous illness etc. were also important methodological considerations and these have been discussed in the sections of the thesis where appropriate.

10.9 Recommendations for Further research

1. As well as investigating the role of psychosocial factors in the recurrence or development of infectious illness, it would be interesting to consider the 'other side of the coin', namely the effect of infectious illness on psychological well being and cognitive performance. Whilst there are some developments in research in this area (e.g. Smith 2000 and Hall and Smith, 1996) these are areas of research worthy of further development. In particular I am not aware of any research that has considered the impact of cold sores on psychological well being and cognitive performance and yet it is intuitively apparent that facial cold sores cause psychological distress to sufferers, particularly adolescent sufferers.
2. The aim in this thesis was to control for the possible confounding influence of health risk behaviours by ensuring that the control groups and the experimental illness groups were well matched on these behaviours. It is well established that one potential route linking psychological stress to immune related disorders is via health risk behaviours which are known to compromise immune status. Further research is required which considers the consequences of stress for health risk behaviour amongst specific groups. For example, do CFS patients utilize more health risk behaviours when they are stressed and which behaviours do they commonly utilize? Are there differences within CFS patients in the health risk behaviours adopted and are these differences translated into increased symptoms of illness.
3. Thirdly and finally, the research in this thesis was based upon quantitative methodology and it would be very interesting to also incorporate qualitative methodology. To consider in more depth and detail subjective experience of chronic illness and perceptions of illness progression and stress related

coping strategies etc. In the glandular fever study, individual perceptions of illness progression were investigated and it was apparent that the literature contains limited information regarding those subjective experiences. This could be developed further and would be a useful addition to the quantitative information currently available.

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APPENDICES

Section One

Examples of Recruitment posters, information sheets, consent letters.

Recruitment Posters.
Information Sheets
Consent Forms
G.P. letters.
Procedures.

Section Two

Questionnaires and Psychosocial Measures.

Questionnaires

Psychosocial Measures

Diary Measures

Section Three

Supplementary Analysis for:-

a. Glandular Fever study
b. HSV study
c. CFS study.

Appendix A1.1 – Example of Recruitment Poster for Glandular Fever Participants.

HAVE YOU EVER SUFFERED FROM

GLANDULAR FEVER

We are currently conducting research
into Glandular Fever and
we are interested in contacting people
who have had this disease within the last
twelve months.

OR

If you are currently suffering from Glandular Fever and have been diagnosed within the last four months.

****

If you are willing to participate please contact

The Health Psychology Research Unit,
Wood Road, Bristol .
or email sfaulkne@glam.ac.uk.

You will be paid £5.00 for your participation which will simply involve completion of questionnaires and computer tasks.

Appendix A1.2 Example of record sheet

GLANDULAR FEVER INFORMATION

NAME: SEX: Male / Female

TERM TIME ADDRESS:

TERM TIME TELEPHONE NO:

ADDRESS AT OTHER TIMES:

TELEPHONE NO.

DATE OF BIRTH:

COURSE:

YEAR OF STUDY:

DATE ILLNESS STARTED:

DATE ILLNESS DIAGNOSED:

BLOOD TEST: POSITIVE NEGATIVE NOT KNOWN

NAME OF G.P.

ADDRESS OF G.P.

TODAY'S DATE:

THANK YOU.

Appendix A1.3 Example of information Sheet for participants

INFORMATION FOR PARTICIPANTS INVOLVED IN THE GLANDULAR FEVER STUDY.

This research is being conducted to investigate the relationship between social and psychological stress and the progression of viral infections, in particular glandular fever. We are also interested in the relationship between illness and performance. We are therefore interested in asking people who have suffered from glandular fever to complete some questionnaires and spend about half an hour carrying out some fairly simple computer tasks.

Criteria

We are interested in students who are either suffering from glandular fever at the moment or who have been diagnosed with the illness within the past 12 months. You will need to be native English speakers and you must be able and willing to return on two or three more occasions (depending upon the current stage of your illness) at approximately three monthly intervals so that we can monitor the progression of your illness, recovery, changes in the nature and level of stress and any changes in performance measures.

All the information you provide will be treated in the strictest confidence and will be recorded using subject numbers and not names. We only require names so that we can send out follow up reminders and confirm the diagnosis of glandular fever with your General Practitioner.

If you are able to fulfil these requirements and participate fully in this study there will be some small financial recompense.

Thank you for your interest and hopefully your continued participation in this project.

Appendix A1.4 Example of Research Procedural Information.

PROCEDURE FOR GLANDULAR FEVER SUBJECTS

When contacted by subject:

1. Give them information sheet about the study - ask them to read it and if they agree to participate .

2. Allocate a number prefixed by the code B (Bristol); C (Cardiff) G (Glamorgan). Record name and date of enquiry next to Code Number in record book.

3. Ask them to complete a. Personal details sheet and
b. G.P. consent letter.
c. consent to participate letter.

4. Give them the Questionnaire Booklet and ask them to complete prior to returning . Please stress that booklets must be completed within one week of doing the tests.

5. Make appointment for returning (within one week of this query if at all possible - if not make sure they know that they need to fill in the booklet within one week of the tests).

Sue Faulkner (tel. 01443 482690 W / 01222 891571 H)

Appendix A1.5 example of consent letter from participant

Date: .....

Dr. .....

.....

.....

.....

.....

Dear Dr. .....

I, ... of (address) .....

.....

.....

have voluntarily agreed to take part in a study to examine the relationship between stress and the progression of glandular fever, which includes individuals who are ill, recovering or back to normal health.

In addition, I have agreed to the researcher contacting you my *General Practitioner/Health Centre Doctor, and I authorise you to disclose details of my relevant medical history, if appropriate. I do not require a copy.

Would you please complete the attached sheet and return it to Ms Susan Faulkner using the enclosed S.A.E. Thank you.

Yours sincerely,

A1.6 Letter for G.P. Confirmation of Glandular Fever

DATE.....

Dr. .....

.....

.....

.....

.....

DEAR Dr. .....,

We are currently running a study on the relationship between stress and the progression of glandular fever including the effects of glandular fever on memory and concentration. Our participants have estimated the date of testing or diagnosis, but clearly the experiment will have greater scientific validity if the approximate date can be confirmed with their doctor. Enclosed is a letter signed by a subject who is your patient. This letter requests you to pass information about blood test dates to me in the enclosed s.a.e. by completing the sheet attached. The patient does not wish to be sent a copy. Naturally, I will preserve the confidential nature of these details, by filing under a code number only. I have also signed a consent form agreeing not to use each person's name in connection with the study.

I would be grateful if you could complete each form and return it as soon as possible. It is important to establish that the subjects have had glandular fever at some time during the last year or so, together with an approximate date for the acute illness. If any person cannot be traced at your surgery, could you please let me know.

Thank you for your help. Your time and trouble is very much appreciated.

Yours sincerely,

SUSAN FAULKNER
SENIOR LECTURER IN PSYCHOLOGY

A1.7 Details of Diagnosis of Glandular Fever from Participants

Code No. _____

ALL THE FOLLOWING INFORMATION MAY NOT BE AVAILABLE, HOWEVER

KINDLY COMPLETE AS MUCH AS YOU CAN.

1. Approximate date of onset of original symptoms of glandular fever:

   (D/M/Y) _____

2. When was the patient first diagnosed as having the illness?

   (D/M/Y) _____

3. Dates when E.B.V.blood tests were taken, most recent first,
   (D/M/Y)

   1. _____ _____ (POS) _____ (NEG)

   2. _____ _____ (POS) _____ (NEG)

   3. _____ _____ (POS) _____ (NEG)

4. Dates of diagnoses of symptom recurrence (e.g. where no blood test or negative test result):

   1. _____

   2. _____

3. _____

5. Any other information relevant to diagnosis of glandular fever in this patient.

Thank you for your help.

Please return to:

S.E. Faulkner
School of Humanities and Social Sciences
University of Glamorgan
Trefforest
Mid Glam CF37 1DL

A1.8 Cold Sore Study. Questionnaire for recruitment of participants

HAVE YOU EVER SUFFERED FROM COLD SORES? YES NO (PLEASE CIRCLE)

DO YOU CURRENTLY SUFFER FROM COLD SORES? YES NO (PLEASE CIRCLE)

IF YES, HOW FREQUENTLY DO YOU GET IT?
ONCE A MONTH
ONCE EVERY TWO MONTHS
ONCE EVERY THREE MONTHS
ONCE EVERY SIX MONTHS
ONCE PER YEAR
OTHER PLEASE SPECIFY?

_____

WHAT TIME OF YEAR DO YOU GET OUTBREAKS?

_____

WHEN WAS YOUR LAST OUTBREAK?

_____

WOULD YOU BE INTERESTED IN TAKING PART
IN A STUDY OF COLD SORES? YES NO (you do not have to suffer from them)

THERE IS NO OBLIGATION BUT THERE WILL BE PAYMENT FOR TAKING PART .....IF YOU WOULD LIKE TO KNOW MORE PLEASE INDICATE HOW AND WHERE YOU CAN BE CONTACTED.

TELEPHONE NUMBER---------- EMAIL NUMBER----------
OR ADDRESS.

THANK YOU FOR YOUR HELP.

A1.9 Example of letter of Consent.

CONSENT FORM: Cold Sore Study

This study entails completing a booklet containing questions regarding your health as well as a number of psychological questionnaires. This should take about 20 minutes.

You need to complete a diary questionnaire, each week for 16 weeks and return these Questionnaires at the end of each week to the University. If you are on holiday or away you can return two the following week.

If you develop a cold sore during the diary period you need to answer the questions on the diary questionnaire regarding your cold sore recurrence and you should contact the research as soon as you can in order that your recurrence can be verified.

Thank you for participating in this study.

Susan Faulkner
Email: sfaulkne@glam.ac.luk
Tel. 01443 482659

Please answer the following questions:

1. Have you read the information given about this study?
2. Do you understand that you are free to withdraw from the study at any time should you wish?
3. Do you agree to take part in this study?

I, the undersigned, voluntarily agree to participate in this study.

---------- ----------
Signed Volunteer Date.

---------- ----------
Signed Investigator Date.

A1.10 Instruction letter for CFS patients

date

Dear

RESEARCH INTO INFECTIONS IN CHRONIC FATIGUE SYNDROME

Thank you again for participating in this study. Here are the instructions.

1. Complete the yellow booklet and week one of the weekly forms and return them to me in the alrge s.a.e. You oly need to complete pages 1,2 and 3 of the weekly forms unless you develop an illness in which case also complete pages 4 and 5.

2. Complete the weekly forms on the same day each week and return them to me in the enclosed self addressed envelopes. Whilst it is important to complete the forms each week you can return them to me fortnightly.

3. Please ensure you include your participant number on each form.

You do not have to put stamps on the envelopes as they are prepaid.

If you have any queries or problems, do not hesitate to contact me on 01443 482659. If I am not there leave your name and number on my answer phone and I will get back to you as soon as I can.

Yours sincerely,

SUSAN FAULKNER

Section Two.

Questionnaires and Psychosocial Measures.

Appendix A2.1 Glandular Fever Questionnaire

GLANDULAR FEVER QUESTIONNAIRE

TIME ONE

NAME
PARTICIPANT NUMBER
CENTRE
DATE OF COMPLETION
DATE RETURNED

PLEASE COMPLETE THIS QUESTIONNAIRE BOOKLET AND BRING IT WITH YOU WHEN YOU RETURN.

NOTE THAT QUESTIONS ARE PRINTED ON BOTH SIDES OF EACH PAGE.

PLEASE ENSURE THAT YOU HAVE ANSWERED ALL QUESTIONS.

THANK YOU FOR YOUR TIME AND CO-OPERATION.

Code Number:

Thank you for agreeing to participate in this study of student health. Please complete the following questions as accurately as you can.

1. Sex Male Female
2. Marital status Single Married Divorced Widowed
3. Date of Birth _____
4. University _____
5. Course _____
6. Year of study _____

General Health/History of Illness

1. Do you suffer from any medical condition (such as diabetes, high blood pressure etc.)?
Please state _____

2. How long have you suffered from the above?

Please state _____

3. Do you suffer from allergies or related illnesses? Yes No

If yes, what type (please tick) ___Asthma ___Eczema ___Hay Fever ___Dust

___Foods ___Chemicals ___Medicines___ Insect stings ___Animal Hair

___ Other (specify) _____

4. Have you had any major illnesses in the past?

Please state _____

5. How would you assess your current state of health (tick one)

_____ Worse than at any stage during the illness
_____ Bad
_____ Bad with some recovery
_____ Recovering with occasional relapses
_____ Almost recovered
_____ Completely recovered

6. In the past twelve months have you suffered from any of the following:

	Very few	About average	Alot
a. colds	.....	.....	.....
b. sore throats	.....	.....	.....
c. bronchitus	.....	.....	.....
d. other (pls state)			
_____	.....	.....	.....

7. Have you suffered from any illness in the last month? Yes No
give details

8. What Medications are you taking at the moment?

Prescribed drugs
(Please state which)_____

_____

Over the counter drugs e.g. paracetamol, cold remedies etc.

_____

multivitamins etc. _____

9. What is the approximate date of the onset of original glandular fever symptoms(D/M/Y)?
_____

10. Did you have a diagnosis from your doctor? a. Yes _____ No _____

If Yes, was this positive ____ (glandular fever) or

negative ____ (not glandular fever)?

What date was this? _____

11. Were you given a blood test for the virus?If Yes, was this

positive ____ (glandular fever) or

negative ____ (not glandular fever)?

What date were you given the test? _____

12. Were you diagnosed as suffering from any other illness? Yes ___ No ___

If yes, give brief details.

13. Have you felt excessively tired or weary during the last week?

Yes _____ No _____

13. Please tick symptoms which you experienced during the first **FOUR WEEKS** of the illness

_____ Sore throat

_____ Fever

_____ Fatigue

_____ Swollen glands

_____ Sweating

_____ Headache

_____ Cough

_____ Loss of Appetite

_____ Swollen or tender spleen

_____ Hot/cold spells

_____ Nausea

_____ Racing Heart

_____ Sore eyes

_____ Muscle aches/cramps

_____ Physical weakness

_____ Indigestion/stomach pain

_____ Sensitive to noise

_____ Sensitive to light

_____ Anxiety/panic

_____ Depression

_____ Loss of concentration

_____ Loss of memory

_____ Insomnia

Appendix A2.2 BACKGROUND INFORMATION FROM COLD SORE PARTICIPANTS.

Code No.

Date

Sex Male Female **Marital Status** Married Single Divorced Widowed

Age _____ **Date if Birth** _____

University _____

Course _____ **Year of Study** _____

Employed Yes No

Type of Employment _____

General Health

Do you sufer from any medical condidition e.g. diabetes, high blood pressure, etc.?

Please state _____

How long have you sufferred from this? _____

Have you ever been diagnosed with Glandular Fever? Yes No

If so please state when _____

Have you sufferred from any other major illnessess in the past Yes No

If so please state what and when _____

Are you currently suffering from any illness? Yes No

If so please state which _____

Do you suffer from allergies or related illnesses? Yes No

If yes, what type? Asthma _____ Eczema _____ Hay Fever _____ Dust _____ Foods _____

Chemicals _____ Medicines _____ Insect stings _____ Animal Hair _____ Other _____

please specify _____

How would you assess your current state of health (tick one)?

Very Ill 1 2 3 4 5 Extreme good health.

In the past year have you sufferred from any of the following?

	Not at all	Very Few	Average	Alot
a. colds	☐	☐	☐	☐
b. sore throat	☐	☐	☐	☐
c. bronchitis	☐	☐	☐	☐
d. flu	☐	☐	☐	☐
e. other pls state.				
_____	☐	☐	☐	☐

What medications are you taking at the moment?

Prescribed drugs (please state) _____

Over the counter drugs _____

Vitamins/minerals _____

Herpes Simplex Questionnaire

1. When did you have your **first** cold sore?

   Month _____ Year _____

2. Have you ever seen a Doctor about your cold sores? Yes No

   When _____

3. Did the Doctor prescribe any medication? Yes No

4. If so what? _____

5. On average, how many episodes of cold sores do you have per year?

   _____

6. Are you currently suffering from an episode of cold sores? Yes No

If Yes, How long ago did this start _____ days?

How severe is this outbreak? Mild 0 1 2 3 4 5 Extremely Severe

7. How many outbreaks have you had in the PAST year? _____

8. When did these outbreaks occur and how long did they last? (From current or last outbreak backwards).

Month of outbreak _____ length (days) _____

Month of outbreak _____ length (days) _____

Month of outbreak _____ length (days) _____

Month of outbreak _____ length (days) _____

Month of outbreak _____ length (days) _____

Month of outbreak _____ length (days) _____

(feel free to add more if neccessary).

9. How severe was your last outbreak?

Mild 0 1 2 3 4 5 Extremely Severe

10. How severe are they generally?

Mild 0 1 2 3 4 5 Extremely Severe

11. What impact does the illness have on your life generally?

1	2	3	4	5
Extremely Negative	Moderately Negative	No Impact	Moderately Positive	Extremely Positive

12. What impact did the **last** episode have on your life in particular?

1	2	3	4	5
Extremely Negative	Moderately Negative	No Impact	Moderately Positive	Extremely Positive

13. What do you think precipitates an outbreak?

Lack of Sleep Not Important 1 2 3 4 5 Extremely Important

Poor General Health Not Important 1 2 3 4 5 Extremely Important

Other Infections (colds etc.) Not Important 1 2 3 4 5 Extremely Important

Poor diet/eating badly	Not Important	1	2	3	4	5	Extremely Important
Too much alcohol	Not Important	1	2	3	4	5	Extremely Important
Menstruation	Not Important	1	2	3	4	5	Extremely Important
UV Sunlight	Not Important	1	2	3	4	5	Extremely Important
Stress	Not Important	1	2	3	4	5	Extremely Important
Other (please state)	Not Important	1	2	3	4	5	Extremely Important

_____

14. What can you do to avoid an outbreak?

_____

_____

_____

15. Do you use any form of treatment once an outbreak has occurred? Yes / No

If Yes, what treatment do you use? _____

_____

Appendix A2.3 . Health Behaviours Questionnaire.

HEALTH RELATED BEHAVIOURS
(please answer re. behaviour prior to onset of illness)

1. How many hours, on average do you **sleep** at night? _____ hours.

2. How often do you feel rested from your nights sleep?

   0=never 1=almost never 2=sometimes 3=fairly often 4=very often

3. How often do you have difficulty either falling asleep or waking early?

   0=never 1=almost never 2=sometimes 3=fairly often 4=very often

4. Would you say that your **diet** was, in general, healthy?

0 =very unhealthy 1 = somewhat unhealthy 2 =neither healthy nor unhealthy 3 =somewhat healthy 4 =very healthy

5. Would you say that you usually eat the right amount of food for you?
   Yes No
   If No, Do you eat too much or too little? **1** = too much **2** = too little.

6. How many cups of caffeinated coffee do you usually drink in a day?

   1 or 2 3 or 4 5 or 6 6+ None

7. Please indicate how often you eat the following foods:

	More than once a day	Once a day	Most days	Once or twice a (3-6) week	Less than once a week	Never
Fresh fruit	6	5	4	3	2	1
Salads/raw veg	6	5	4	3	2	1
Fresh cooked veg	6	5	4	3	2	1
Red meat	6	5	4	3	2	1
Fried foods	6	5	4	3	2	1
Crisps (or similar)	6	5	4	3	2	1
Chocolate/sweets	6	5	4	3	2	1
Biscuits/cakes	6	5	4	3	2	1
Breakfast cereal	6	5	4	3	2	1
Cheese	6	5	4	3	2	1
Eggs	6	5	4	3	2	1
fish or poultry	6	5	4	3	2	1

Butter	6	5	4	3	2	1
low fat spread	6	5	4	3	2	1

8. How much milk do you drink per day? _____

   Is this skimmed milk = 1 semi skimmed milk = 2 full fat milk = 3.

9. Would you say that you are :

0 = a non drinker **1** = a very occasional drinker **2** = an occasional drinker **3** = a regular drinker

10. Would you say that you are :

0 = a light drinker **1** = a moderate drinker **2** = a heavy drinker

11. On how many days have you had an alcoholic drink in the week before you felt ill? ____

12. What did you have to drink the week before you felt ill?

How many half pints of beer/lager _____
How many single measure spirits _____
How many glasses of wine _____

13. Would you say that this drinking was : 0 = reasonably typical
1 = less than usual
2 = more than usual

14. Do you smoke at least one cigarette a day? No Yes

15. On average how many cigarettes do you smoke? _____
(if less than one put 1).

16. How often do you take walks, runs or jogs in good weather?
0 = never or very infrequently **1** = sometimes **2** = frequently

17. How often do you swim or do aerobic exercise?
0 = never or very infrequently **1** = sometimes **2** = frequently

18. How often do you do physical work around the home?
0 = never or very infrequently **1** = sometimes **2** = frequently

19. How often do you participate in energetic sports?
0 = never or very infrequently **1** = sometimes **2** = frequently

20. How often do you participate in golf, bowling, snooker etc.)?
0 = never or very infrequently **1** = sometimes **2** = frequently

21. How often do you watch television? **0** = once a week or less
1 = several times/week
2 = daily, less than 2 hours
3 = 2 to 4 hours/daily

4 = more than 4 hours/day

PSYCHOSOCIAL MEASURES.

A2.4	Life Events Scale
A2.5	Daily Hassles Scale
A2.6	Perceived Stress Scale
A2.7	Beck Depression Inventory
A2.8	Trait Anxiety
A2.9	Positive and Negative Mood
A2.10	Profile of Fatigue Related Symptoms
A2.11	Self Esteem Scale
A2.12	Social Support Scale
A2.13	Health locus of control
A2,14	Ways of Coping Scale
A2.15	Life Orientation Test (LOT)

DIARY MEASURES

APPENDIX A2.16 COLD SORE DIARY QUESTIONNAIRE

WEEKLY CHECKLIST

PLEASE COMPLETE THIS CHECKLIST AT THE END OF EACH WEEK. TRY TO COMPLETE IT AT THE SAME TIME EACH WEEK.

ONCE YOU HAVE COMPLETED THE CHECKLIST, PLEASE RETURN IT TO ME AS SOON AS YOU CAN – EITHER IN THE HUMANITIES OFFICE OR TO ME IN FOREST HALL 323

DATE..... TIME.....

HAVE YOU SUFFERED FROM ANY ILLNESS THIS WEEK? YES NO

PLEASE SPECIFY:

_____

IF YES, PLEASE COMPLETE THE GENERAL SYMPTOM CHECKLIST ATTACHED.

DO YOU FEEL YOU MAY BE COMING DOWN WITH AN ILLNESS? YES / NO

HAVE YOU HAD ANY APPEARANCE OF COLDSORES THIS WEEK? YES / NO

IF YES, PLEASE COMPLETE THE COLDSORE CHECKLIST ATTACHED.

DO YOU FEEL AS IF AN EPISODE OF COLDSORE IS IMMINENT? YES / NO / NOT SURE

HOW HAVE YOU BEEN FEELING IN GENERAL THIS WEEK?

1	2	3	4	5
EXTREMELY UNWELL	FAIRLY UNWELL	NEITHER WELL NOR UNWELL	FAIRLY WELL	EXTREMELY WELL

HAVE YOU SLEPT WELL THIS WEEK?

MORE THAN USUAL SAME AS USUAL BETTER THAN USUAL

HOW MUCH ALCOHOL HAVE YOU DRUNK THIS WEEK?

LESS THAN USUAL SAME AS USUAL MORE THAN USUAL

HAVE YOU HAD A STRESSFUL WEEK IN GENERAL?

1	2	3	4	5
EXTREMELY STRESSFUL	FAIRLY STRESSFUL	NEITHER	FAIRLY UNSTRESSFUL	EXTREMELY UNSTRESSFUL

HOW WOULD YOU DESCRIBE YOUR MOOD THIS WEEK IN GENERAL?

1	2	3	4	5
EXTREMELY NEGATIVE	FAIRLY NEGATIVE	NEITHER NEG NOR	FAIRLY POSITIVE	EXTREMELY POSITIVE

HAS ANYTHING HAPPENED TO DISTRESS YOU **OR** MAKE YOU FEEL GOOD THIS WEEK? YES NO
Please list any significant events (indicate whether good or bad):

_____

_____

Please list any minor irritations:_____

_____

DURING THE LAST WEEK, HAVE YOU FELT THAT YOU HAVE COPED WELL WITH ALL THE THINGS YOU HAVE HAD TO DO?

NOT AT ALL WELL 1 2 3 4 5 EXTREMELY WELL

PLEASE INDICATE WHICH OF THE FOLLOWING SYMPTOMS YOU HAVE FELT THIS WEEK.

No symptoms _____ Runny/blocked nose _____ Cough _____

Flu like symptoms _____ Headache _____ Lack of confidence _____ Fatigue _____

Muscle aches _____ Sore throat _____ Nausea _____ Unusually hot or cold _____

Worried / anxious _____ Lack of concentration _____ Depression _____

Other (please state)

PERIOD STARTED _____ FINISHED _____

IF YOU DO DEVELOP A COLD SORE, PLEASE COMPLETE THE FOLLOWING CHECKLIST.

WHEN DID THE COLD SORE APPEAR? DAY _____ AM / PM

WHEN DID IT GO? DAY _____ AM / PM

HOW SEVERE IS THE OUTBREAK?

VERY MILD	MODERATELY MILD	MODERATELY SEVERE	EXTREMELY SEVERE

HOW PAINFUL IS THE OUTBREAK?

MILD	MODERATE	SEVERE	VERY SEVERE

WHAT IMPACT HAS THIS HAD ON YOUR LIFE THIS WEEK?

1	2	3	4	5
EXTREMELY NEGATIVE	FAIRLY NEGATIVE	NEITHER NEG NOR POSITIVE	FAIRLY POSITIVE	EXTREMELY POSITIVE

HAVE YOU TAKEN ANY MEDICATION? If yes please state what.

_____

_____

HAVE YOU TAKEN ANY OTHER STEPS TO TREAT THE COLD SORE?

_____

_____

ANY OTHER COMMENTS e.g. has it stopped you from doing anything or affected your life in any way?

_____

Is there anything you believe precipitated this outbreak?

NOW COMPLETE THE SYMPTOM CHECKLIST.
If you do experience an outbreak of cold sore, please get in touch with me as soon as you can.
email – sfaulkne@glam.ac.uk
tel – 01443 482659 or 01222 891571

SYMPTOM CHECKLIST FOR OTHER ILLNESS

What illness have you suffered from this week? _____

_____

When did it start? Day _____ AM / PM

When did it stop? Day _____ AM / PM

HOW SEVERE IS THE ILLNESS?

VERY MILD	MODERATELY MILD	MODERATELY SEVERE	EXTREMELY SEVERE

WHAT IMPACT HAS THIS HAD ON YOUR LIFE THIS WEEK?

1	2	3	4	5
EXTREMELY NEGATIVE	FAIRLY NEGATIVE	NEITHER NEG NOR POSITIVE	FAIRLY POSITIVE	EXTREMELY POSITIVE

HAVE YOU TAKEN ANY MEDICATION? If yes please state what.

_____

_____

HAVE YOU TAKEN ANY OTHER STEPS TO TREAT THE ILLNESS? Please specify.

_____

_____

ANY OTHER COMMENTS e.g. has it stopped you from doing anything or affected your life in any way?

_____

_____

Is there anything you believe precipitated this outbreak? etc.

_____

NOW COMPLETE THE SYMPTOM CHECKLIST.

If you are uncertain about anything relating to these questions, please get in touch with me as soon as you can.

e mail – sfaulkne@glam.ac.uk
tel -01443 482659 or 01222 891571.

Thank you

PLEASE COMPLETE THIS CHECKLIST IF YOU HAVE HAD A COLD SORE **OR** IF YOU HAVE BEEN ILL THIS WEEK.

	not present	**mild**	**moderate**	**severe**	**very severe**
1. Physical weakness	1	2	3	4	5
2. Excessive fatigue	1	2	3	4	5
3. Legs feeling heavy	1	2	3	4	5
4. Muscle pain	1	2	3	4	5
5. Pain in chest	1	2	3	4	5
6. Painful joint	1	2	3	4	5
7. Nausea	1	2	3	4	5
8. Indigestion	1	2	3	4	5
9. Bloated stomach	1	2	3	4	5
10.Wind	1	2	3	4	5
11. Sore throat	1	2	3	4	5
12. Headache	1	2	3	4	5
13. Earache	1	2	3	4	5
14. Sore eyes	1	2	3	4	5
15. Sensitive to noise	1	2	3	4	5
16. Sensitive to light	1	2	3	4	5
17. Feeling hot/cold	1	2	3	4	5
18. Sweating	1	2	3	4	5
19. Shivering	1	2	3	4	5
20. Swollen glands	1	2	3	4	5
21. Racing heart	1	2	3	4	5

	not present	mild	moderate	severe	very severe
22. Insomnia	1	2	3	4	5
23. Depression	1	2	3	4	5
24. Anxiety/panic feelings	1	2	3	4	5
25. Loss of concentration	1	2	3	4	5
26. Loss of memory	1	2	3	4	5
27. Allergies	1	2	3	4	5
28. Other _____	1	2	3	4	5
_____	1	2	3	4	5

APPENDIX A2.17 CFS DIARY QUESTIONNAIRE
Subject no ..... Week no.....

WEEKLY CHECKLIST

PLEASE COMPLETE THIS CHECKLIST AT THE END OF EACH WEEK. TRY TO COMPLETE IT AT THE SAME TIME EACH WEEK.

ONCE YOU HAVE COMPLETED THE CHECKLIST, PLEASE RETURN IT TO ME AS SOON AS YOU CAN IN THE ENLCOSED S.A.E.

DATE..... TIME.....

HAVE YOU SUFFERED FROM ANY INFECTIOUS ILLNESS THIS WEEK, SUCH AS COLD, INFLUENZA, BRONCHITIS, TONSILITUS, ETC?

YES NO

PLEASE SPECIFY WHICH INFECTIOUS ILLNESS AS PRECISELY AS YOU CAN.

_____

HAVE YOU SUFFERED FROM ANY OTHER TYPE OF ILLNESS THIS WEEK?

YES NO

PLEASE SPECIFY _____

IF YES TO ANY ILLNESS, PLEASE COMPLETE THE ADDITIONAL QUESTIONS AND SYMPTOM CHECKLIST ATTACHED.

DO YOU FEEL YOU MAY BE COMING DOWN WITH AN ILLNESS?

YES NO

HAVE YOU TAKEN ANY MEDICATION THIS WEEK? YES NO
IF YES, PLEASE SPECIFY_____

_____

HOW HAVE YOU BEEN FEELING IN GENERAL THIS WEEK?

1	2	3	4	5
EXTREMELY UNWELL	FAIRLY UNWELL	NEITHER WELL NOR UNWELL	FAIRLY WELL	EXTREMELY WELL

HAVE YOU SLEPT WELL THIS WEEK?

MORE THAN USUAL SAME AS USUAL BETTER THAN USUAL

HOW MUCH ALCOHOL HAVE YOU DRUNK THIS WEEK?

LESS THAN USUAL SAME AS USUAL MORE THAN USUAL

HAVE YOU HAD A STRESSFUL WEEK?

1	2	3	4	5
EXTREMELY STRESSFUL	FAIRLY STRESSFUL	NEITHER	FAIRLY UNSTRESSFUL	EXTREMELY UNSTRESSFUL

HOW WOULD YOU DESCRIBE YOUR MOOD THIS WEEK IN GENERAL?

1	2	3	4	5
EXTREMELY NEGATIVE	FAIRLY NEGATIVE	NEITHER NEG NOR	FAIRLY POSITIVE	EXTREMELY POSITIVE

HOW MUCH EXERCISE HAVE YOU TAKEN THIS WEEK?

LESS THAN USUAL SAME AS USUAL MORE THAN USUAL

HAS ANYTHING HAPPENED TO DISTRESS YOU **OR** MAKE YOU FEEL GOOD THIS WEEK? YES NO

Please list any significant events (indicate whether good or bad):

_____

_____

_____

_____

_____

Please list any minor irritations:_____

_____

_____

_____

DURING THE LAST WEEK, HAVE YOU FELT THAT YOU HAVE COPED WELL WITH ALL THE THINGS YOU HAVE HAD TO DO?

NOT AT ALL WELL 1 2 3 4 5 EXTREMELY WELL

PLEASE INDICATE WHICH OF THE FOLLOWING SYMPTOMS YOU HAVE FELT THIS WEEK.

No symptoms _____

Runny/blocked nose	not at all	moderately	extremely
Cough	not at all	moderately	extremely
Indigestion	not at all	moderately	extremely
Flu like symptoms	not at all	moderately	extremely
Headache	not at all	moderately	extremely
Lack of confidence	not at all	moderately	extremely
Physical fatigue	not at all	moderately	extremely
Mental fatigue	not at all	moderately	extremely
Muscle aches	not at all	moderately	extremely
Sore throat	not at all	moderately	extremely
Nausea	not at all	moderately	extremely
Unusually hot or cold	not at all	moderately	extremely
Worried / anxious	not at all	moderately	extremely
Lack of concentration	not at all	moderately	extremely
Trouble remembering things	not at all	moderately	extremely
Depression	not at all	moderately	extremely

Other(please state)

_____	not at all	moderately	extremely
_____	not at all	moderately	extremely

IF YOU HAVE SUFFERED FROM ANY ILLNESS THIS WEEK, PLEASE ANSWER THE FOLLOWING:

What illness have you suffered this week?

_____

When did it start? Day _____ AM / PM
When did it stop? _____ AM / PM

HOW SEVERE IS THE ILLNESS THIS WEEK?

VERY MILD	MODERATELY MILD	MODERATELY SEVERE	EXTREMELY SEVERE

WHAT IMPACT HAS THIS HAD ON YOUR LIFE THIS WEEK?

1	2	3	4	5
EXTREMELY NEGATIVE	FAIRLY NEGATIVE	NEITHER NEG NOR POSITIVE	FAIRLY POSITIVE	EXTREMELY POSITIVE

HAVE YOU TAKEN ANY MEDICATION? If yes please state what.

_____

_____

HAVE YOU TAKEN ANY OTHER STEPS TO TREAT THE ILLNESS? Please specify.

_____

_____

ANY OTHER COMMENTS e.g. has it stopped you from doing anything or affected your life in any way?

_____

_____

Is there anything you believe precipitated this illness?

_____

_____

NOW COMPLETE THE SYMPTOM CHECKLIST.
If you are uncertain about anything relating to these questions, do not hesitate to get in touch with me. Susan Faulkner, tel 01443 482659. If I am not there please leave a message on the ansaphone and I will get straight back to you.

PLEASE COMPLETE THIS CHECKLIST IF YOU HAVE BEEN ILL THIS WEEK.

	not present	mild	moderate	severe	very severe
1. Physical weakness	1	2	3	4	5
2. Excessive fatigue	1	2	3	4	5
3. Legs feeling heavy	1	2	3	4	5
4. Muscle pain	1	2	3	4	5
5. Pain in chest	1	2	3	4	5
6. Painful joint	1	2	3	4	5
7. Nausea	1	2	3	4	5
8. Indigestion	1	2	3	4	5
9. Bloated stomach	1	2	3	4	5
10.Wind	1	2	3	4	5
11. Sore throat	1	2	3	4	5
12. Headache	1	2	3	4	5
13. Earache	1	2	3	4	5
14. Sore eyes	1	2	3	4	5
15. Sensitive to noise	1	2	3	4	5
16. Sensitive to light	1	2	3	4	5
17. Feeling hot/cold	1	2	3	4	5
18. Sweating	1	2	3	4	5
19. Shivering	1	2	3	4	5
20. Swollen glands	1	2	3	4	5
21. Racing heart	1	2	3	4	5
22. Insomnia	1	2	3	4	5

	not present	mild	moderate	severe	very severe
23. Depression	1	2	3	4	5
24. Anxiety	1	2	3	4	5
25. Panic feelings	1	2	3	4	5
26. Loss of concentration	1	2	3	4	5
27. Loss of memory	1	2	3	4	5
28. Allergies	1	2	3	4	5

please state _____

29. Sneezing	1	2	3	4	5
30. Runny nose	1	2	3	4	5
31. Chills	1	2	3	4	5
32. Phlegm	1	2	3	4	5
33. Skin disorder	1	2	3	4	5

please state _____

34. Other _____	1	2	3	4	5
_____	1	2	3	4	5

Any other comments:

Glandular Fever Study Supplementary Analyses

APPENDIX A3.1

Table of symptoms showing differences between the glandular fever participants, the recovered glandular fever participants and the healthy control group in two locations.

Symptom	Bristol Healthy	Glamorgan Healthy	All Glandular Fevers	Recovered Glandular Fevers
Physical weakness	5% 2	22% 11	44% 30	8% 1
Fatigue	5% 2	10% 5	48% 33	17% 2
Legs heavy	2% 1	6% 3	28% 19	17% 2
Muscle Pain	10% 4	24% 12	21% 14	17% 2
Pain in chest	0%	4% 2	3% 2	8% 1
Painful joints	2% 1	2% 1	9% 6	0
Nausea	0%	6% 3	4% 3	0
Indigestion	2% 1	4% 2	7% 5	0
Bloated stomach	2% 1	10% 5	10% 7	17% 2
Wind	0%	6% 3	10% 7	8% 1
Sore Throat	7% 3	12% 6	44% 30	8% 1
Headache	7% 3	18% 9	49% 33	42% 5
Ear Ache	0%	6% 3	9% 9	0
Sore Eyes	22% 9	20% 10	27% 18	17% 2
Noise sensitivity	0%	8% 4	10% 7	8% 1
Light sensitivity	2% 1	10% 5	9% 6	0
Hot / Cold	2% 1	8% 4	22% 15	0
Sweating	2% 1	8% 4	18% 12	0
Shivering	0%	0%	3% 2	0
Swollen Glands	0%	0%	35% 24	8% 1
Racing Heart	0%	0%	9% 6	8% 1

Insomnia	2% 1	2% 1	13% 9	8% 1
Depression	2% 1	10% 5	15% 10	17% 2
Anxiety/Panic	2% 1	8% 4	16% 11	17% 2
Loss of concentration	7% 3	16% 8	54% 37	33% 4
Loss of memory	0%	8% 4	15% 10	17% 2
Allergies	30% 12	4% 2	7% 5	0
Other	5% 2	16% 8	18% 12	25% 3
Total mean	1.25	2.48	5.57	3

APPENDIX A3.2

Analysis for the control of possible confounding variables

Allergies

The analysis on allergies was carried out firstly on the whole group and then on the glandular fever group and the control group separately. Firstly, symptoms and effects of illness were considered and then the effect on psychosocial variables.

In the glandular fever group mean total symptoms were 4.63 (sd=2.84) for non allergic and 5.53 (sd=4.03) for allergic. a small difference which was not significant (P<0.31.). The allergic group suffered more from sore eyes,(allergy group mean=1.26 (1.1)/mean non allergic group=0.2 (0.2),P<0.02 and sensitivity to light allergy group mean=1.24 (1.0)/non allergic group 0.4 (0.3),P<0.04).. For psychosocial variables there were differences in life orientation with the allergic group having a more pessimistic outlook, mean scores were 30.81 (6.36) and 27.92 (6.67) ($p < 0.04$). The allergic group were very slightly lower in self-esteem (56.8 (12.16) vs. 54.0 (10.17)) (P<0.07).

In the control group there were few real differences. The non-allergic group were significantly higher in fatigue (0.14 (0.2) vs. 0.03 (0.1) $p < 0.01$) although for 'other symptoms' the allergic group were higher (0.02 (0.1) vs. 0.21 (0.2), $P < 0.002$) but for total symptoms there was little difference (1.65 (1.1) vs. 2.10(1.8)) and this was non-significant.

There were few differences between the allergic and non-allergic groups overall and it was concluded that there was no reason to treat those suffering from allergies any differently.

Confirmed cases

Again, there were few significant differences between the confirmed and non-confirmed cases. The non-confirmed cases were usually cases where the notes could not be traced or the G.P. had either refused to confirm or not written back. There were no significant differences between the groups in total symptoms but the non-confirmed suffered more: (a) indigestion (mean confirmed=0.18 (sd 0.39) / mean non confirmed =0.021 (sd=0.02), $P < 0.02$), (b) sweating (mean confirmed= 0.29 (0.47)/mean non confirmed (0.10 (0.31) ($p < 0.06$). There were no differences in reported severity of the glandular fever or length of illness and there were no differences in infectious illnesses in past year, or allergic status. For psychosocial variables differences were not significant apart from the following variables: (a) non-confirmed cases were higher in emotional distress confirmed mean=54.26 (25.4)/non confirmed mean =39.58 (17.37) ($p < 0.01$) and (b) lower in self esteem (confirmed mean =47.67 (12.97) / non confirmed mean=55.60 (11.07) ($P < 0.02$). In conclusion there were no large differences emerging for either the non-confirmed cases or the allergic status cases and therefore the analysis continued including these participants.

APPENDIX A3.3

Table Mean Score (sd) for glandular fever participants and the healthy control group on Coping Strategies.

Variables	Healthy N=31	All Glandular Fevers N=52	Significance
Coping Strategies			
Problem solving	14.71 (3.90)	13.59 (3.46)	Ns
Confrontative	12.55 (2.55)	12.0 (3.26)	ns
Seek social support	14.71 (3.33)	14.42 (3.63)	ns
Positive readjustment	13.17 (3.54)	12.0 (4.23)	ns
Accept responsibility	8.84 (2.58)	8.72 (2.75)	P<0.04
Self control	15.94 (3.17)	15.52 (3.64)	ns
Escape Avoidance	14.07 (4.38)	15.74 (4.14)	P<0.08
Distancing	12.81 (3.27)	11.86 (2.94	ns
Social Support			
ISEL A	35.58 (4.73)	34.09 (5.50)	ns
ISEL T	34.52 (4.22)	34.27 (4.55)	ns
ISEL S	31.60 (3.42)	29.48 (4.34)	P<0.08
ISEL B	34.71 (4.28)	34.12 (4.36)	ns
TOTAL ISEL	136.23 (14.37)	132.34 (15.73)	ns

APPENDIX A3.4

Analysis of differences between the categories of glandular fever (acute, mids, chronics) considering different cut off points

Groups were compared on current symptoms, effect and progression of illness using the above two sets of criteria.

First analysis :	**Second analysis:**
Group A	**Group B**
recovered (n=13)	recovered (n=13)
acute 0-3 months (n=20)	acute 0-2 months (n= 13)
mids 4-9 months (n=11)	mids 3-6 months (n=12)
chronic 10mths+ (n=19)	chronics 7 mths+ (n=25)

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APPENDIX A3.5

Table to show differences between glandular fever patients at different stages of their illness (acute, mids and chronics) and recovered glandular fever patients on a sample of current symptoms using different categorisations.

Current Symptoms (column percentages)	Recovered	Acute Glandular Fevers		Mids Glandular Fevers		Chronics Glandular Fevers	
Categorisation		**A**	**B**	**A**	**B**	**A**	**B**
Weakness	8%	58%	54%	64%	58%	35%	46%
Exc fatigue	17%	58%	39%	46%	33%	41%	36%
Legs heavy	17%	42%	39%	27%	33%	12%	18%
Muscle Pain	17%	16%	15%	36%	25%	18%	22%
Sore Throat	8% (1)	42%	46%	55%	50%	65%	59%
Headache	42%	42%	38%	82%	75%	41%	46%
Sore eyes	17%	32%	23%	27%	33%	6%	13%
Hot/Cold	0	16%	8%	27%	33%	29%	27%
Sweating	0	16%	15%	18%	17%	12%	14%
Shivering	0	11%	7%(1)	0	8%(1)	0	0
Swollen Glands	0	37%	54%	36%	25%	41%	36%
Depression	17%	16%	15%	18%	25%	6%	5%
Anxiety	17%	26%	23%	18%	25%	0	5%
Loss concentration	33%	52%	39%	63%	83%	65%	59%
Loss memory	17%	11%	8%	0	8%	18%	14%
Allergies Now	0	11%	15%	0	0	12%	9%
Extreme tiredness in past week	23%	79%	79%	54%	64%	58%	58%
Wake early/ difficulty sleeping	31%	40%	43%	27%	33%	16%	17%

Past month bad	23%	53%	46%	36%	58%	26%	25%

APPENDIX A3.6

Frequency Of Infectious Illness In Glandular Fever Participants And Healthy Controls.

A. Colds

Colds in last 12 months	Glandular Fever Participants	Healthy Controls
Few colds	9 17%	43 54%
Average no. of colds	26 48%	28 35%
A lot of colds	19 35%	9 11%

B. Upper Respiratory Tract Infections URTIs

URTIs in last 12 months	Glandular Fever Participants	Healthy Controls
Few URTIs	8 (15%)	48 (61%)
Average no. of URTIs	16 (29%)	24 (30%)
A lot of URTIs	31 (56%)	7 (9%)

APPENDIX 3.7

Mean Scores (sd) for Glandular Fever Groups and the Healthy control group on Psychosocial Measures (Social Support and Coping Strategies) co-varying negative affect (NA).

Variable	G.fvr Nosymps (N=32)	G.fvr Acutes (N=6)	G.fvr Chronics (N=10)	Healthy Controls (N=30)	*F Value & Significance*
ISELA ns	33.9(5.9)	34.8 (2.3)	35.1(5.3)	36.1 (3.8)	*0.81 P<0.51*
ISELT ns	34.2 (5.1)	32.0 (4.0)	36.2 (3.2)	34.9 (3.8)	*1.81 P<0.13*
ISELS ns	30.7 (4.3)	28.3 (4.2)	29.4(5.3)	31.8 (3.2)	*1.73 P<0.14*
ISELB ns	34.1 (4.7)	34.0 (3.9)	34.3(4.7)	34.9(4.3)	*0.65 P<0.63*
Total Social Support ns	132.8 (16.9)	129.2 (12.9)	134.6 (16.1)	137.5 (12.7)	*1.04 P<0.39*
Coping Strategies: Problem Solving ns	12.9 (3.2)	14.5 (3.6)	14.3(3.7)	14.8(4.0)	*1.11 P<0.36*
Confrontive Coping ns	10.9 (2.9) - -	14.2 (2.32) -	13.6(3.86) -	12.5(2.58)	*3.02 P<0.02*
Social Support*	13.1 (3.0) **	15.8 (4.0)	17.3 (3.9) **	14.8(3.4)	*3.18 P<0.01*
Positive Readjustmnt ns	10.8 (3.2)	12.5 (4.1)	13.8(5.9)	13.0(3.5)	*1.95 P<0.10*
Escape Avoidance ns	15.4 (4.59)	16.5 (3.45)	14.7(2.83)	13.7(4.04)	*1.30 P<0. 27*
Distance ns	12.2 (2.9)	10.7 (3.5)	11.6(3.2)	12.0 3.3)	*1.25 P<0.29*

Differences between the groups on social support and coping strategies were not significant.

Cold Sore Study Supplementary Analysis

APPENDIX 3.8

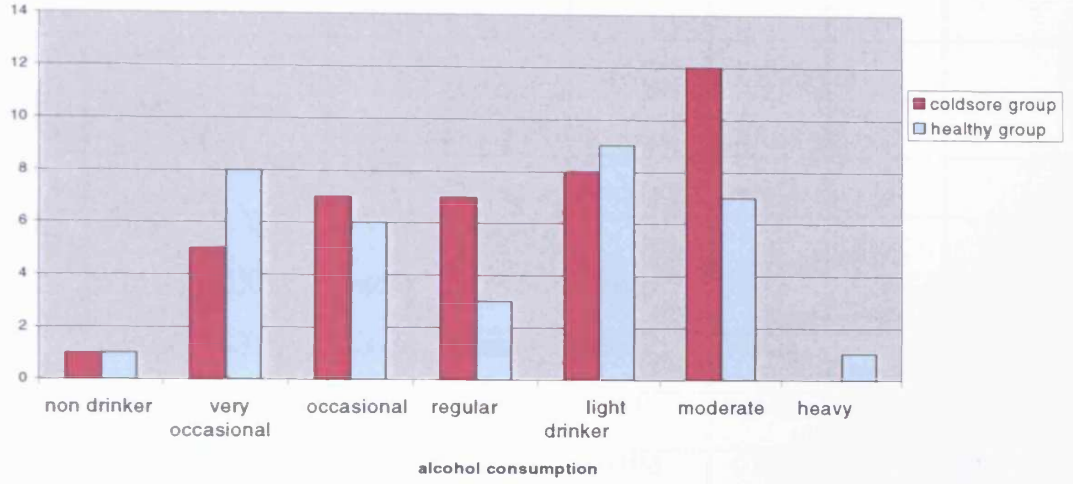
Table to show differences between the Coldsore Participants and the HealthyControl Participants on general health

	cold sores	healthy	Sig.
chronic medical condition.	3 (16%)	2 (11%)	ns
allergies	8 (40%)	6 (33%)	ns
Current state of health:			ns
1. Very ill	0	0	
2.	0	0	
3.	6 (35%)	2 (11%)	
4.	11 (53%)	11 (61%)	
5. Extreme good health	3 (15%)	5 (28%)	
Mean	**3.85**	**4.17**	
Medication Use.			
a. prescribed drugs	4 (20%)	2 (11%)	ns
b. over the counter drugs	4 (20%)	1 (6%)	*
c. vitamins/minerals	11 (55%)	4 (22%)	*

APPENDIX 3.9

Health Behaviours.

Figure: Comparison of alcohol consumption in coldsore sufferers and controls



APPENDIX 3.9

The table below shows a comparison of the amount of exercise in the two groups

	Never		Sometimes		Frequent	
	clds	hlthy	clds	hlthy	clds	hlthy
Jogging	2 (10%)	1 (6%)	11(55%)	10(56%)	7(35%)	7 (39%)
Swim/ aerobic	4(20%)	3(17%)	6(30%)	7(39%)	10(50%)	8(44%)
Physical work	3(15%)	2(11%)	12(60%)	12(67%)	5(25%)	4(22%)
Energetic sport	7(35%)	6(33%)	8(40%)	6(33%)	5(25%)	6(33%)
Non Energetic	15(75%)	14(78%)	4(20%)	3(17%)	1(5%)	1 (6%)

APPENDIX 3.10

Correlations for Cold sores: All Participants (N=38)

	neg_le	pos_le	tot_le	intensit	freq	cum_sev	pss	freqill	wkghlth
neg_le	1.0000								
pos_le	0.0820	1.0000							
tot_le	0.8186	0.6397	1.0000						
intensit	0.3065	-0.1344	0.1589	1.0000					
freq	0.3847	0.2887	0.4631	0.5159	1.0000				
cum_sev	0.3643	0.1633	0.3751	0.6735	0.9576	1.0000			
pss	0.6299	0.1219	0.5560	0.5550	0.6616	0.6538	1.0000		
freqill	0.6429	0.2027	0.6126	0.4019	0.5863	0.5347	0.8195	1.0000	
wkghlth	-0.2899	-0.0204	-0.2354	-0.0783	-0.0870	-0.0383	-0.2782	-0.1383	1.0000

	pos_mood	neg_mood	bdi	trait	ed	fatigue	cd	ss	se	freqill	wkghlth
pos_mood	1.0000										
neg_mood	-0.6169	1.0000									
bdi	-0.4360	0.7225	1.0000								
trait	-0.5997	0.7772	0.8495	1.0000							
ed	-0.5850	0.8465	0.8326	0.8409	1.0000						
fatigue	-0.5059	0.7669	0.6505	0.7471	0.8893	1.0000					
cd	-0.4028	0.7233	0.6950	0.7276	0.8276	0.8559	1.0000				
ss	-0.3364	0.6631	0.7807	0.7371	0.7526	0.7064	0.7177	1.0000			
se	0.3981	-0.7064	-0.7519	-0.8001	-0.6929	-0.6142	-0.6242	-0.7218	1.0000		
freqill	-0.3242	0.6130	0.8164	0.7126	0.7185	0.6445	0.6237	0.6739	-0.6679	1.0000	
wkghlth	0.2936	-0.1740	-0.0832	-0.2307	-0.2827	-0.2357	-0.1811	-0.1701	0.2131	-0.1383	1.0000

	ISELA	ISELT	ISELS	ISELB	tot_isel	intloc	pohloc	chloc	tot_hloc	freqill	wkghlth
ISELA	1.0000										
ISELT	0.0967	1.0000									
ISELS	-0.0160	0.3647	1.0000								
ISELB	0.2087	0.4907	0.6229	1.0000							
tot_isel	0.5594	0.6722	0.6499	0.8434	1.0000						
Intloc	0.2815	-0.0011	-0.0391	0.3167	0.2468	1.0000					
Pohloc	0.6813	0.3551	-0.2162	-0.0214	0.3485	0.3260	1.0000				
Chloc	0.6115	0.1339	-0.3061	-0.1509	0.1669	0.3316	0.6080	1.0000			
tot_hloc	0.6730	0.2143	-0.2379	0.0616	0.3282	0.6992	0.8343	0.8178	1.0000		
Freqill	-0.1057	0.0041	-0.4067	-0.5287	-0.3806	-0.1561	0.2020	0.3250	0.1576	1.0000	
wkghlth	0.2024	0.1078	0.1391	0.3113	0.2940	-0.3033	0.0843	-0.1497	-0.1490	-0.1383	1.0000

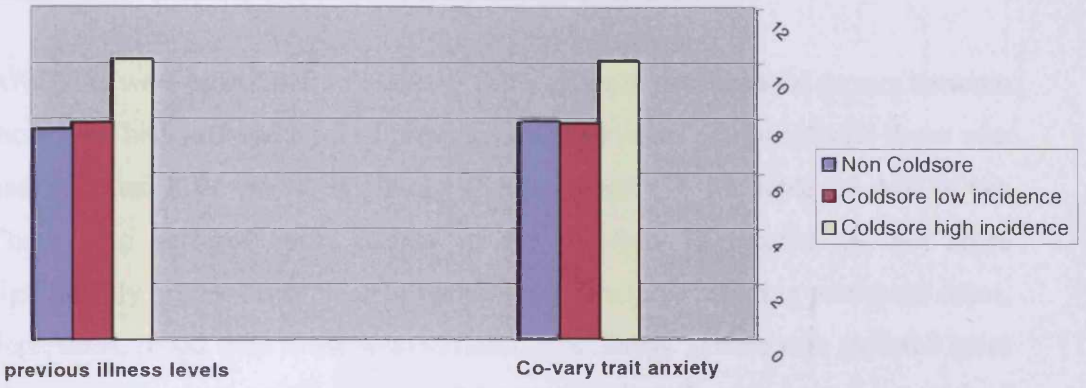
	probsolv	confcop	socspt	posread	accresp	slfcon	Escavd	Dist	lot	Freqill
probsolv	1.0000									
confcop	0.3691	1.0000								
socspt	0.3153	0.4061	1.0000							
posread	0.3412	0.6080	0.3655	1.0000						
accresp	0.3593	0.5838	0.1060	0.6269	1.0000					
Slfcon	0.1728	0.5943	0.2612	0.6728	0.7234	1.0000				
escavd	0.0784	0.6147	0.3213	0.7190	0.6354	0.7254	1.0000			
dist	-0.0158	0.2248	0.2186	0.4431	0.5481	0.5622	0.6226	1.0000		
lot	0.1881	-0.1680	0.0885	-0.3976	-0.5118	-0.4409	-0.5817	-0.4993	1.0000	
Freqill	0.1129	0.3628	0.1243	0.5252	0.4574	0.4592	0.5594	0.4308	-0.5336	1.000
Wkghlth	0.447	0.0703	0.1612	-0.1869	-0.0254	-0.086	-0.2499	-0.1662	0.3879	-0.1383

Key for abbreviations used in the above correlation matrix.

neg_le = negative life events	**pos_mood** = positive mood
pos_le = positive life events	**neg_mood** = negative mood
tot_le = total life events	**Bdi** = Beck Depression Inventory
Intensity = intensity of hassles	**Trait** = Trait anxiety
cum_sev = cumulative severity	**Ed** = Emotional Difficulty
Pss = perceived social stress	**Fatigue** = Fatigue
Freqill = frequency of illness	**cd** = Cognitive difficulty.
Wkghlth = weekly general health	**Ss** = Somatic Symptoms
ISELA = Social Support A	**Se** = Self Esteem
ISELT = Social Support T	**Intloc - Internal health locus of control**
ISELS = Social Support S	
ISELB= Social Support B	
tot_isel = Social Support (total)	

APPENDIX 3.11

Figure A3.11 showing the frequency of previous illness and the frequency of cold sore recurrence



These results indicate a relationship between the frequency of cold sore recurrence and the previous incidence of other infectious illness. This relationship remained significant when trait anxiety was co-varied. It can be seen from this analysis that those who suffered from a greater number of recurrences of cold sores in the past twelve months were also more vulnerable to the development of more frequent viral infections, largely colds and influenza. This group are high on psychosocial measures of stress and depression however this relationship is not simply a consequence of negative affect (as measured by trait anxiety) influencing their responses to questionnaires or the perceived severity of their illness. The differences between those suffering frequent recurrence of cold sores and psychosocial measures was significant even when trait anxiety and previous illness were co-varied. So, it does not appear that previous illness is the important factor influencing levels of psychosocial stress and depression and the subsequent development of illness. Those who subsequently suffer more illness

(i.e. the high frequency cold sore group) do so independently of their previous illness levels.

APPENDIX 3.12

Within the cold sore group only, participants were divided by the number of illnesses (other than cold sores) in the previous 12 months

ANOVAs were calculated to measure differences in psychosocial factors between those who had suffered a lot of previous other illnesses compared with those who had suffered little previous illness (See Appendix 1 for table of ANOVAs). Those who suffered more illness in the previous 12 months did not score significantly higher on standard psychosocial measures incuding perceived stress, depression, mood than those who suffered less illness. Those who suffered more illness in the previous 12 months did report a significantly greater number of negative life events and used coping strategies relying on confrontation and problem solving. Generally, however, there was little effect of previous illness on psychosocial measures in the cold sore group.

APPENDIX 3.12

The relationship between (a) previous illness and scores on the psychosocial measures and (b) the relationship between psychosocial measures and subsequent development of illness . Participants were divided on a median split (median = 7; mean=7.8)

Table: comparison of psychosocial measure scores in health controls with higher and lower levels of previous illness

Psychosocial Measure	Low Previous Illness n=11 Mean (sd)	Higher Previous Illness n=6 Mean (sd)	Significance
Perceived Stress	13.1 (3.1)	20.7 (6.5)	0.004
Negative Life Events	0.3 (0.6)	2.5 (2.2)	0.005
Total Life Events	1.5 (1.3)	3.7 (3.3)	0.06
B.D.I.	2.0 (0.9)	4.5 (2.3)	0.004
Hassles: Cum. Severity	8.6 (4.6)	23.3 (16.2)	0.06
Frequency	6.1 (2.5)	14.0 (8.9)	0.01
Negative Mood	8.9 (7.0)	13.7 (8.4)	n.s.
Emotional Difficulty	17.2 (4.0)	27.2 (11.3)	0.01
Cognitive Difficulty	12.7	17.2	0.01
Somatic Symptoms	19.5 (2.9)	24.5 (3.8)	0.09 n.s.
Self Esteem	66.7 (4.0)	52.0 (12.3)	0.002
Life Orientation	38.1 (4.9)	32.5 (6.4)	0.06
Total Isel	127.7 (3.3)	126.0 (8.0)	n.s.
Coping Strategies: Problem solving	15.5 (3.4)	14.3 (3.5)	n.s.
Conf coping	10.4 (2.7)	13.5 (3.1)	0.04
Social Support	14.1 (1.9)	15.2 (3.1)	n.s.
Positive Readjust	10.4 (1.9)	11.8 (3.1)	n.s.
Accept Respons	5.4 (1.4)	8.2 (1.5)	0.001
Slf Conf.	11.4 (2.5)	15.7 (2.4)	0.004
EscapeAvoidance	0.3 (1.8)	12.5 (2.9)	0.01
Distancing	8.3 (3.1)	8.7 (1.5)	n.s.

APPENDIX 3.13

The control group were divide into (a) those who developed two or more illnesses during the period and (b) those who developed one or no illness, and the relationship between psychosocial measures at baseline and the subsequent development of less or more illness was considered.

Table: the relationship between baseline psychosocial measures and subsequent development of illness over the diary period in healthy controls

Psychosocial Measure	**One or less illnesses n=13 Mean (sd)**	**Two or more illnesses n=4 Mean (sd)**	**Significance**
Perceived Stress	13.7 (5.2)	25.4 (3.8)	P<0.003
Covary previous ill	14.3 (1.8)	18.9 (2.4)	n.s
Covary NA	14.9 (2.0)	18.4 (2.4)	n.s.
Negative Life Events	0.69 (0.3)	2.25 (1.9)	n.s.
Total Life Events	2.0 (1.8)	3.0 (2.3)	n.s.
B.D.I.	2.2 (1.5)	5.3 (2.1)	P<0.001
Covary prev.illness	2.5 (0.8)	4.2 (1.6)	P<0.04
Covary n.a.	2.6 (0.9)	3.8 (1.8)	n.s.
Hassles: Cum. Severity	11.92 (7.4)	20.0 (9.9)	n.s.
Frequency	7.46 (2.3)	13.5 (7.8)	n.s.
Negative Mood	8.6 (5.4)	17.0 (6.4)	P<0.05
Covary prev ill	10.0 (1.3)	15.2 (3.2)	n.s.
Covary n.a.	10.0 (1.3)	12.6 (4.3)	n.s.
Emotional Difficulty	17.4 (6.2)	31.5 (9.9)	P<0.001
Covary prev ill	18.3 (1.3)	28.5 (3.3)	P<0.02
Covary n.a.	19.6 (2.6)	24.2 (4.3)	n.s.
Cognitive Difficulty	13.7 (5.4)	16.3 (6.6)	n.s.
Somatic Symptoms	14.5 (5.3)	26.8	P<0.03
Covary prev ill	20.1 (2.1)	24.9	n.s.
Covary trait anx.	20.6 (2.2)	23.2	n.s.
Self Esteem	65.8 (25.0)	47.8 (30.1)	P<0.005
Covary prev. ill.	64.3 (3.2)	32.5 (3.5)	P<0.01
Covary Trait anx.	63.2 (4.5)	56.2 (4.3)	n.s.

Total Isel	127.54	125.75	n.s.
Life Orientation	38.15	29.50	P<0.006
Covary prev. ill	37.53	31.53	P<0.08
Covary trait anx.	36.52	34.78	n.s.
Coping Strategies:			
Problem solving	15.1 (6.2)	15.6 (5.8)	n.s.
Conf coping	10.9 (4.2)	13.3 (4.3)	n.s.
Social Support	14.2 (4.4)	15.5 (4.5)	n.s.
Positive Readjust	10.5 (3.8)	12.3 (3.2)	n.s.
Accept Respons	5.8 (2.1)	8.3 (1.5)	.02
Slf Conf.	11.8 (3.4)	16.5 (5.2)	.005
EscapeAvoidance	9.6 (2.1)	13.0 (4.3)	.02
Distancing	8.2 (1.8)	9.0 (2.6)	n.s.

CFS SUPPLEMENTARY ANALYSIS

Appendix 3.14

Table A3.14 definition of abbreviations used in tables

cd= cognitive difficulty	**Freq infec** – Frequency of recurrence of infectious illness during the diary period.
ss= somatic symptoms	**Freq oth ill** – Frequency of recurrence of other illness during the diary period
se = self esteem	Tot week stress – total weekly stress (low=high stress)
ed = emotional difficulty	Tot gen hlth – total general health (diary) (low= poor health)
tot isel - Total Score on Social Support Scale	Totwkmd – total weekly mood (low=neg mood)
trait = Negative Affect	Towksym2 – total weekly cough
negle= negative life events	Towksym3 – total weekly flu symptoms
intensity=intensity of daily hassles	Towksym4 – total weekly headaches
freq= frequency of daily hassles	Towksym8 - total weekly mental fatigue
cumsev=cumulative severity of daily hassles	
pss= perceived stress scale	
bdi=Beck depression inventory	
negmood= negative mood	

Tables.showing correlation matrix for baseline measures and subsequent diary measures for the chronic fatigue patients only.

	cd	ss	se	fatigue	ed	tot_isel	trait
Freq infec	0.1386	-0.2068	0.5025	-0.1895	-0.1528	0.0052	0.0684
Freq oth ill	0.3374	0.1202	0.2422	0.2627	-0.1687	-0.2022	-0.1590
Tot week Stress	**-0.7724 ***	-0.4331	0.2476	-0.3326	-0.1820	0.3300	-0.5752
Tot gen hlth	-0.4812	-0.4236	0.0765	-0.4560	-0.1959	0.0410	-0.0917
Towksym2	0.0890	0.3374	-0.3426	0.0945	0.2533	0.0649	0.0687
Towksym3	0.0031	-0.2476	-0.1389	-0.3901	0.2125	0.2282	0.2709
Towksym4	0.0589	-0.1166	-0.1067	0.0242	-0.0733	-0.1839	-0.2300
towksym7	0.3980	0.3495	**0.7137 ***	0.6110	0.3932	0.3732	0.2483
Towksym8	-0.0851	-0.1783	-0.2727	0.4915	0.2316	-0.1717	0.3737
Tot weekly mood	**-0.7429 ***	**-0.8413 ***	0.5005	-0.6267	-0.4996	0.2707	**-0.7107 ***
Weekly bad events	0.4059	0.3412	0.1662	0.0962	0.0320	-0.2348	0.2494

	neg_le	intensit	freq	cumsev	pss	bdi	negmood
Freq infec	0.0848	0.1820	0.0137	-0.0824	-0.0301	0.0134	-0.1960
Freq oth ill	0.4109	-0.0665	0.1084	0.0583	0.0878	-0.0741	-0.3215
Totwk stress	**-0.6815***	-0.4942	-0.4794	-0.5049	-0.5789	-0.3816	-0.1040
Totgen health	-0.1407	-0.1509	-0.1544	-0.2094	-0.0955	0.0520	0.0779
Towksym2 cough	0.0915	0.5287	0.0918	0.2417	0.1235	0.4708	0.2853
Towksym3 indigestion	-0.0412	0.3570	-0.1290	-0.0814	-0.1276	-0.0788	0.2685
Towksym4 Flu symps	-0.2175	-0.3776	-0.2744	-0.3844	-0.3512	-0.0148	-0.2279
Towksym7 Physical fatigue	0.2384	0.2432	0.6145	0.5670	0.3756	0.1188	0.2733
Towksym8 Mental fatigue	0.4537	0.4911	0.5935	**0.6147 ***	0.4796	0.2051	0.0793
Tot weekly mood	**-0.7272 ***	-0.2902	-0.6079	**-0.6662***	**-0.7400 ***	-0.5345	-0.4165
Weekly bad events	0.4412	0.4291	0.3478	0.3994	0.3093	0.1186	-0.0735

There were few significant correlations overall. Negative life events was correlated with total weekly stress over the diary period. Perceived stress was approaching significance with total weekly stress.

Cumulative Severity of hassles was significantly associated with mental fatigue over the diary period.

Negative life events, perceived stress and cumulative severity of hassles – all three stress measures taken at baseline, were significantly correlated with negative mood over the diary period.

Cognitive difficulties measured at baseline were significantly associated with total weekly stress and self esteem was correlated with physical fatigue over the diary period.

Cognitive difficulty, somatic symptoms and trait anxiety were significantly associated with total weekly mood. The same correlations were conducted separately for the healthy control group and are shown in the tables below.

Tables.showing correlation matrix for baseline measures and subsequent diary measures for the health group

	neg_le	intensit	freq	cumsev	pss	bdi	negmood
Freqinf	0.2206	0.0754	0.6136	**0.6758***	0.3617	**0.8656***	**0.7169***
Freqotil	0.3281	-0.1667	0.3578	-0.0197	0.1571	**0.6887***	0.3382
Totwkstr	**-0.6651***	-0.1740	**-0.6887***	**-0.7085 ***	**-0.7559***	**-0.8000***	**-0.7467***
Totgenhl	-0.5743	-0.0077	**-0.7289***	**-0.7674 ***	-0.6272	**-0.9214***	**-0.7682***
Towksym2	0.3004	-0.1823	**0.8109***	**0.8557 ***	0.5687	**0.9560***	**0.8630***
Towksym3	0.5535	-0.1667	**0.6679 ***	**0.6489 ***	**0.8423 ***	**0.7098 ***	**0.7626 ***
Towksym4	0.3054	0.3727	0.4315	0.4748	0.2246	**0.7844 ***	0.5140
Towksym7	0.5502	0.2695	**0.6536 ***	**0.7769 ***	0.5077	**0.8906 ***	**0.6471***
Towksym8	0.5808	0.2107	**0.6392 ***	**0.7030 ***	0.5897	**0.8514 ***	**0.6503 ***
Totwkmod	-0.5574	0.2236	**-0.8298 ***	**-0.7705 ***	**-0.8206 ***	**-0.8552***	**-0.8667***
Wkbd events	0.5225	-0.0144	0.6289*	**0.7429 ***	**0.7207 ***	0.5963	0.6338

	cd	ss	se	fatigue	ed	tot_isel	trait
Freqinf	**0.7658***	**0.6988***	**-0.7228***	**0.9265***	**0.6684 ***	-0.2503	0.3370
Freqotil	**0.6472***	**0.9647***	-0.4023	**0.7309***	0.5906	**-0.0765 ***	0.1868
Totwkstr	**-0.8451***	-0.5834	**0.7358***	**-0.7762***	**-0.8518***	**0.6730 ***	**0.7640***
Totgenh	**-0.8727 ***	**-0.7907***	**0.7449***	**-0.8915***	**-0.9277***	0.4778	**0.6520***
Totwksym2	**0.8236 ***	**0.7488***	**-0.8157***	**0.9506***	**0.8358***	-0.0536	0.5386
Totwksym3	**0.7823***	0.3562	**-0.7594***	0.5942	**0.9001***	**-0.7634 ***	**0.8766***
Towksym4	**0.8001***	**0.8668***	-0.6203	**0.8600***	**0.6467***	-0.2794	0.3037
Towksym7	**0.9596***	**0.7991***	**-0.6839***	**0.8955***	**0.8480***	-0.4492	0.5336
Towksym8	**0.9650***	**0.7011***	**-0.7036***	**0.8189***	**0.8858***	-0.5645	0.6343
Totwkmod	**-0.7836***	-0.5889	**0.8071***	**-0.7557***	**-0.9457***	0.5491	**0.8012***
wkbdnts	**0.7464 ***	0.1683	-0.6331	0.4896	**0.7399 ***	-0.6133	**0.6845***

*(NB: critical value for 15 cases at .01 significance =-0.64 to 1.00 or -0.64to1.0)

Baseline psychosocial measures were more likely to be correlated with subsequent stress and health scores during the diary period. They were also associated with the likelihood of developing infectious illness during the diary period. These correlations, however, largely disappeared when negative affect was co-varied.